# The potential application of supercritical fluids to the production of coatings for pharmaceutical products

Broadbent, Andrew

*Award date:*
1999

*Awarding institution:*
University of Bath

# The Potential Application of Supercritical Fluids to the Production of Coatings for Pharmaceutical Products.

Submitted by Andrew Broadbent
for the degree of Ph.D.
of the University of Bath
1999







ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

# Abstract

Supercritical carbon dioxide has been recognised as an effective solvent for many years; far better than traditional thermodynamic theory predicts. Recently it has demonstrated potential as a solvent in a number of industrial applications, especially for extraction of flavour and aroma compounds in the food industry, as it is cheap, non-toxic and relatively inert. The principle objective of this project was to investigate the feasibility of using supercritical carbon dioxide ($SCCO_2$) as a solvent for the application of pharmaceutical coatings.

An experimental rig was designed and constructed to measure the solubility of polymers of pharmaceutical relevance in $SCCO_2$. The rig could be operated at pressures up to 600 bar and temperatures up to 200°C. Suitability of the rig for acquiring solubility data was verified by measuring the solubility of naphthalene in $SCCO_2$, and comparing the results obtained with published data.

Initial work proved that the widely used pharmaceutical coating material, hydroxypropylmethylcellulose was effectively insoluble in $SCCO_2$. Low molecular weight poly (DL-lactide) however was shown to have a solubility of over 1 wt% in $SCCO_2$ at 600 bar and 55°C. For most of the polymers studied the solubility in $SCCO_2$ increased with increasing pressure and temperature, but decreased as the molecular weight of the polymer increased.

In attempting to predict the solubilities of the materials studied in $SCCO_2$, the Peng Robinson and Soave Redlich Kwong equations of state were used together with the Joback method to estimate the properties of the polymers. This was not found to be successful.

It was concluded that while $SCCO_2$ alone is not a suitable solvent for use with common high molecular weight polymers, it may have the potential to be a useful solvent for processing those exotic low molecular weight polymers, which are not water soluble.

## Acknowledgements

The author would like to thank the following:

David Merrifield, the late Norman Orr, and John Lovegrove of SmithKline Beecham Pharmaceuticals for providing both funds and technical advice to allow the project to progress this far, and for constructing the equilibrium cell used in the experimental rig.

Richard England, Barry Crittenden, and John Staniforth of the University of Bath for advice, discussions and criticisms.

Merv Newnes, Mac Forsyth and Elaine Odgers, for assistance in buying and constructing the experimental rig.

BBSRC, for financial assistance, Award Number 94560557.

And finally Debbie, I couldn't have done it without you.

# Contents

# Chapter 1. Introduction

Solvents are used widely in the pharmaceutical industry for processing excipients, for example in granulation processes. A major area of use is in the application of coatings to tablets and other pharmaceutical products. Typically hydrocarbon and chlorinated hydrocarbon solvents are used, but both the environmental aspects of waste solvents and the health implications of residual solvent remaining in pharmaceutical products are of concern. These have led the pharmaceutical industry to seek cleaner, less harmful "environmentally friendly" solvents with which to replace hydrocarbons. Supercritical carbon dioxide has been identified as a possible replacement. Carbon dioxide is non-toxic, and more environmentally friendly than typical hydrocarbons and in the supercritical state it is recognised as a good solvent, indeed far better than traditional thermodynamics predicts. This project has applied itself to the investigation of the potential of carbon dioxide in the supercritical state for use within the pharmaceutical industry.

## 1.1. Current Methods of Coating Tablets

The methods by which tablets are coated have changed little since the 1950's. To apply the coatings, tablets are tumbled and warmed in a pan coater, whilst the coating, dissolved in a suitable solvent, is sprayed onto the tablets. The tumbling motion prevents the tablets from sticking together. Warm air is blown in to evaporate the solvent leaving the coating material as a surface layer on the dried tablets. An alternative is to use a fluidized bed coater, where the tablets, as the name suggests, are fluidized with a current of warm air as the coating solution is applied.

These processes often use hydrocarbon and chlorinated hydrocarbon solvents such as acetone, alcohols and dichloromethane (Seitz *et al.*, 1986). This results in considerable volatile organic compound (VOC) emissions to the atmosphere. There is considerable worldwide pressure to reduce the environmental impact of all manufacturing processes. Increased stringency of environmental legislation, particularly the Environmental Protection Act (1990) (Department of the Environment, 1991), has meant that harmful waste products emitted to land, water or atmosphere have had to be decreased. There are further worries about the effects of

residual solvent on patients taking the tablets (Porter *et al.,* 1982). It is therefore necessary to develop new methods for coating tablets to eliminate or reduce hydrocarbon emissions.

The pharmaceutical industry focused on water as an environmentally friendly and non-toxic alternative to hydrocarbon solvents. This led to a number of new coating materials being developed that would dissolve or form a suitable suspension in water. This action has been moderately effective in reducing the use of hydrocarbons in the production of tablets, but has not been without problems.

Many drug materials are hydrophilic and will degrade in the presence of water. Tablets containing these drugs require a sealing coat, applied using a hydrocarbon solvent, before the main water based coating can be applied. This results in increased processing time and cost. Water is less volatile than traditional solvents, which can result in an inferior quality of coating, as well as increasing processing times and energy input during the drying stage.

Advances in pharmaceutical technology have lead to the development of enteric and controlled release coating materials. By their very nature it is often not possible to apply these coatings using water as the solvent. Controlled release materials such as poly (DL-lactide) degrade slowly by hydrolysis in the presence of water, and thus must be kept dry. Enteric coatings such as polymers based on polymethylmethacrylate are insoluble in water, and must be applied with hydrocarbons such as acetone and propanol.

## 1.2. Supercritical Carbon Dioxide

A solvent which has not previously been considered for applying pharmaceutical coatings is supercritical carbon dioxide. It was noted well over a century ago that a gas above its critical temperature would not condense to form a liquid, no matter how much the pressure was increased. These "dense gases", or supercritical fluids as they are now known, were found to be better solvents than conventional thermodynamics

predicts (Robin and Vodar, 1953). For example, carbon dioxide at 50°C and 600 bar has a density of 800 kg $m^{-3}$, more typical of that of a liquid, and has dissolving powers similar to some hydrocarbon liquids (McHugh and Krukonis, 1994).

The aim of this work was to conduct initial investigations into the potential of supercritical carbon dioxide as a solvent for use by the pharmaceutical industry. Supercritical carbon dioxide was selected for a number of reasons:

1. It is "environmentally friendly", relative to hydrocarbons
2. It is non-toxic and relatively inert
3. It has been proved an effective solvent within the food industry
4. The solvent power is easily varied, and it has a low critical temperature
5. It has shown promise as a solvent in the paint industry.

These benefits are discussed in detail in the following sections.

### 1.2.1. The Environmental Benefits of Carbon Dioxide

When compared to the hydrocarbons and chlorinated hydrocarbons used currently by the pharmaceutical industry, carbon dioxide is environmentally friendly. The atmosphere naturally contains carbon dioxide which is essential for plant growth. Hydrocarbons, when released into the atmosphere as VOCs are pollutants. They react photochemically in the lower atmosphere to produce ozone, a gas which causes respiratory problems, and they are powerful greenhouse gases, believed to be implicated in global warming. Chlorinated hydrocarbons are yet more damaging. They are toxic, and harmful in the lower atmosphere, and it is believed that they contribute to the destruction of the protective ozone layer when they reach the upper atmosphere (Verschueren, 1983). It is only recently that the harmful effects of VOCs have been recognised, and steps have been taken to control the release of these polluting materials into the environment. The Environmental Protection Act (EPA) of 1990 lays down the principle that waste should be reduced or eliminated at source rather than relying on end of pipe solutions. By attempting to replace VOCs with a

material which is far less polluting, i.e. carbon dioxide, this project is following the philosophy of the EPA.

It is true, however, that carbon dioxide is a greenhouse gas and there has been considerable effort to reduce carbon dioxide emissions on a world scale. International environmental summits have been held at Rio (1992), Montreal (1994), and more recently Kyoto (1997) to discuss this issue, and to set targets limiting greenhouse gas emissions. These were aimed at reducing the vast quantity of carbon dioxide released from burning fossil fuels, rather than the small amount which would be required for processing pharmaceuticals. It should be possible to recycle carbon dioxide for use in these types of processes. The whole issue of utilizing carbon dioxide produced for example by burning fossil fuels or by fermentation processes has been discussed by Edwards, (1995). It has been hypothesized in this work that the carbon dioxide produced naturally during the fermentation of alcoholic drinks could be recovered for use in a supercritical coating system.

### 1.2.2. The Inert, Non-Toxic Nature of Carbon Dioxide

Carbon dioxide is a stable, relatively inert compound and is unlikely to react chemically with drug materials. Carbon dioxide therefore has a considerable advantage over water, the solvent the pharmaceutical industry is using increasingly to replace organic solvents. Many drug materials will react with water, causing them to degrade; a reason often given for coating tablets is to protect them from atmospheric water. Aqueous coating systems cannot be used on tablets containing these materials. Carbon dioxide is non-toxic and hence harmless to humans. At high concentrations it can act as an asphyxiant by displacing oxygen, but at low levels it is harmless to health.

### 1.2.3. The Use of Carbon Dioxide in the Food Industry

Supercritical carbon dioxide has been used as a solvent in the food industry for some time (Eggers, 1978). A number of processes were patented in the 1970's for decaffeinating coffee using supercritical carbon dioxide as a solvent (Zosel, 1974;

Roselius *et al.,* 1974). More recent research within the food industry has focused on the use of supercritical carbon dioxide as a solvent for extracting fats, oils, flavours and aromas from a wide range of food materials including nuts, fish, herbs and spices (Friedrich, 1984; Gaspar *et al.,* 1997).

### 1.2.4. The "Tuneability" of Supercritical Carbon Dioxide

The solvent power of supercritical carbon dioxide can be varied widely by manipulating pressure and temperature, hence, in theory it should be possible to deposit a film from a supercritical solution by reducing the pressure by a relatively small amount. This means that the drying stage could be omitted and the carbon dioxide easily recycled. Further, carbon dioxide has a low critical temperature, 31.1°C; any process using supercritical carbon dioxide can be run at moderate temperatures which are unlikely to have adverse effects on active drug components.

### 1.2.5. The Use of Carbon Dioxide in the Paint Industry

Recently published work has documented the successful use of supercritical carbon dioxide, mixed with traditional solvents, for the application of car paints, (Busby *et al.,* 1990). There is an obvious similarity between spray painting and coating tablets; while the materials used differ the spraying action is comparable. This work has also been driven by the reliance on hydrocarbon solvents and the strong environmental pressures to reduce VOC emissions.

## 1.3. Measuring Solubility in Supercritical Carbon Dioxide

In order for a successful system of applying coatings to pharmaceutical products to be developed, the coating materials of interest must be soluble in supercritical carbon dioxide to a reasonable degree. There is no published data of this nature and therefore the first step in assessing the efficacy of the process was to design and build equipment to measure the solubility of the pharmaceutical excipients in supercritical carbon dioxide. There were many different methods of doing this identified in the

literature which are described in Section 2.4. They all involved creating a supercritical solution at the temperature and pressure of interest, taking care to ensure the solution and solute were at equilibrium. The supercritical solution was then separated, usually by reducing the pressure and allowing the solute to precipitate. The amount of carbon dioxide and solute used was measured and the solubility calculated.

For this work a flow-type rig was developed which was capable of operating at temperatures up to 200°C and pressures up to 600 bar. In this, the supercritical solution was formed continuously by passing carbon dioxide at the desired temperature and pressure through a bed containing the solute. The solution was separated by allowing the pressure to drop to atmospheric pressure over a throttle valve. The precipitated solute was collected and weighed, and the flow of carbon dioxide measured. Care was taken to ensure an equilibrium was reached between the carbon dioxide and the solute, and that all precipitated solute was collected.

The full design specification and rig operation are described in Chapter 3, while the mechanical design and validation of the equilibrium cell, which was made in house, is detailed in Appendix A. Once built, the rig was validated by measuring the solubility of naphthalene in supercritical carbon dioxide. The results obtained were found to be in close agreement, generally within 4%, of those reported by Tsekhanskaya *et al.* (1964).

## 1.4. Materials Used

Initially, five materials were chosen for study from the vast array of actual and potential pharmaceutical excipients available for use in coating tablets. These were: hydroxypropylmethylcellulose, a ubiquitous water soluble polymer, currently widely used for coating tablets; poly (DL-lactide), poly (DL-lactide-co-glycolide) and poly-β-hydroxybutyric acid, materials with the potential to be used as controlled release coatings; and Eudragit® RL100, a co-polymer of poly methylmethacrylate, used as an enteric coating.

Rather than studying a large number of different excipients, it was decided to use the limited time and resources available to study three of the above materials, poly (DL-lactide), poly (DL-lactide-co-glycolide) and Eudragit® RL100, in more detail. By using samples of poly (DL-lactide) of different molecular weights, the effect of this on solubility in supercritical carbon dioxide could be investigated. The solubility of lactic acid, the starting material used in the manufacture of poly (DL-lactide), was also measured to allow comparison between a polymer, and a chemically similar small molecule.

## 1.5. Presentation of Results

The solubility results are presented as isotherms and isobars in Chapter 4, and the trends observed are discussed. Chapter 4 also characterises the physical changes of the pharmaceutical excipients following the solubility measurements. The possible reasons for the solubility trends measured are discussed in Chapter 5, and hypotheses are offered as to the factors which may affect the solubility of polymers in supercritical carbon dioxide. The solubilities of the solutes studied have been correlated with the density of the carbon dioxide, and these trends discussed.

## 1.6. Modelling Work

It was recognised that measuring solubilities experimentally is time consuming and requires complex and expensive equipment, therefore in Chapter 6, an attempt has been made to predict the solubilities of the materials studied. This modelling work was based on the equality of fugacities of the solute in the solid phase and in solution, and used well known equations of state to estimate the fugacity coefficient of the solute in solution. For the polymers, where physical property data such as vapour pressure, molar volume and acentric factor was not available, the method of Joback was used to estimate these. The predicted isotherms obtained, together with comparisons with experimental data are presented in Chapter 6.

## 1.7. Conclusions

The significance and implications of both the experimental results, and the predicted solubilities obtained are discussed in Chapter 7. Opinions are offered as to the feasibility of using supercritical carbon dioxide as a solvent for the application of pharmaceutical coatings. Recommendations for further work are made. These focus on methods of increasing the solubility of polymers in supercritical carbon dioxide and on potential alternative uses of supercritical carbon dioxide in the pharmaceutical industry.

# Chapter 2. Literature Review

This novel research attempts to use supercritical fluid technology in the application of pharmaceutical coatings. No references were found in the literature about applying pharmaceutical coatings with supercritical fluids, and therefore the literature covering pharmaceutical coating has been reviewed separately. As described below, (Section 2.1) the methods currently used for applying pharmaceutical coatings have changed little over the last 30 - 40 years. Supercritical fluid technology on the other hand has been the subject of much research recently, in a wide range of different areas, but especially in the area of extraction in the food industry, Section 2.7.1. Due to the large advances in supercritical fluid technology in the last few years, the literature in this area has been considered in considerably greater depth.

## 2.1. Coating Pharmaceutical Products

Many pharmaceutical products, especially tablets are coated as the final stage in the manufacturing process. This is done at a significant cost but is necessary for a number of reasons (Seitz *et al.,* 1986):

- To mask the taste, odour, or colour of the drug.
- To provide physical and chemical protection for the drug.
- To control the release of the drug from the tablet.
- To protect the drug from the gastric environment with an acid resistant enteric coating.
- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
- To improve pharmaceutical elegance by use of colours, and contrasting printing.

Sugar coatings on pills have been used since the 1600's, and became popular in the mid 1800's. Large scale coating pans were developed at this time.

The first film coated tablets were marketed in 1953, and around this time considerable work was done developing and improving the pan coating process.

Perforated coating pans, allowing high air flow such as the Accela-Cota system resulted, enabling film coatings to be applied quickly and reliably. Wurster (1953) patented an air suspension coater which operated on a fluidised bed principle. Both these systems are currently used commercially by pharmaceutical manufacturers.

The materials needed for film coating include the film forming resin and a solvent to deliver the resin to the tablet. Plasticisers, to modify the mechanical properties of the film, and colourants, to improve the appearance of the tablets are often used. The common resins used to form film coatings have been discussed by Porter *et al.* (1982) and Seitz *et al.* (1986). The most popular are cellulose ethers such as hydroxypropylmethylcellulose (HPMC), and hydroxypropylcellulose (HPC). Other polymers such as polyvinylpyrrolidone (PVP) and polyethyleneglycols are also used. Often two or more resins may be used to obtain a film with the required chemical and mechanical properties.

Resins must be dissolved in a solvent in order to be applied to the tablets. Solvents currently used include alcohols, dichloromethane, acetone, and water. Solvent properties such as volatility and viscosity have a considerable effect on the quality of the tablet coating. A solvent blend is often used in order to optimize these properties (Porter *et al.,* 1982).

To apply the coatings, tablets are tumbled and warmed in a pan coater. The coating, dissolved in the solvent, is sprayed onto the tablets as they are tumbled. Warm air is blown in to evaporate the solvent so drying the tablets. Coating tablets is a skilled process and needs to be carefully controlled. The speed of rotation of the pan, the rate at which the coating is sprayed, the degree of atomization of the spray, and the flow rate and temperature of the drying air can all affect the quality of the finished coating.

Problems with the current methods of coating stem from the solvents used to apply the coatings. There is a move to reduce the amount of hydrocarbon and chlorinated hydrocarbon solvents used in industry in general (Crittenden and Kolaczkowski, 1995). Hydrocarbons tend to be derived from oil, an expensive non-renewable

resource. They react photo-chemically in the lower atmosphere to produce ozone, and they are greenhouse gases, thought to increase global warming if released into the atmosphere. Chlorinated hydrocarbons are also thought to destroy ozone in the upper atmosphere, which has the effect of increasing the amount of harmful UV light reaching the earth's surface.

In the coating process some solvent residue remains on the tablets, and is ingested by the patient. This is undesirable as chlorinated hydrocarbons have toxic effects. For example, dichloromethane is an irritant, can damage vital organs such as the liver, and is thought to be a carcinogen (IRPTC, 1992).

Water is increasingly being used as a solvent, as it is harmless, is in plentiful supply, and is not a pollutant. There are however other problems associated with using water as a solvent. The quality of coatings obtained is reduced, compared to those obtained with organic solvents, and the length of time taken for the coating process is considerably longer, due to the lower volatility of water. Many drugs react with water hence requiring a sealing coat to be applied first before the water based coat can be used. Many coating resins are not water soluble and thus cannot be applied in this way.

The aim of this project is to investigate the potential of supercritical carbon dioxide as a solvent for the application of pharmaceutical coatings. Carbon dioxide is cheap, readily available and non-toxic. It is a reasonably inert gas, and is unlikely to react with drugs. Environmentally, carbon dioxide is a greenhouse gas, and there has been much discussion at the international environmental summits at Rio, (1992), Montreal, (1994) and Kyoto, (1997) about reducing carbon dioxide emissions. These discussions were centred around the production of large quantities of carbon dioxide by burning fossil fuels, rather than the release of comparatively tiny amounts from supercritical fluid processes.

Recycling carbon dioxide has been discussed from an environmental and economic point of view by Edwards (1995). He pointed out that the carbon dioxide produced for use in areas such as chemical and fertilizer manufacture, and the food and

beverage industry was also very small compared to that released by burning fossil fuels. He also noted that the cost of recovering carbon dioxide from power station flue gas, while significant, was not so high as to exclude this area from further study. It would therefore seem feasible to use recycled carbon dioxide for supercritical processes.

The solubility of the coating resins in supercritical carbon dioxide over a range of temperatures and pressures is not known, hence the first stage in this project is to determine the solubility of a number of coating materials.

## 2.2. Supercritical Fluids

There are three basic states of matter, solid, liquid and gas, and by changing the temperature and pressure, all pure substances can be made to change between these three states, provided no decomposition occurs. Phase changes occur at distinct points, e.g. melting and boiling points for substances at atmospheric pressure. This behaviour can be represented on a phase diagram, as shown for carbon dioxide in Figure 2.1.

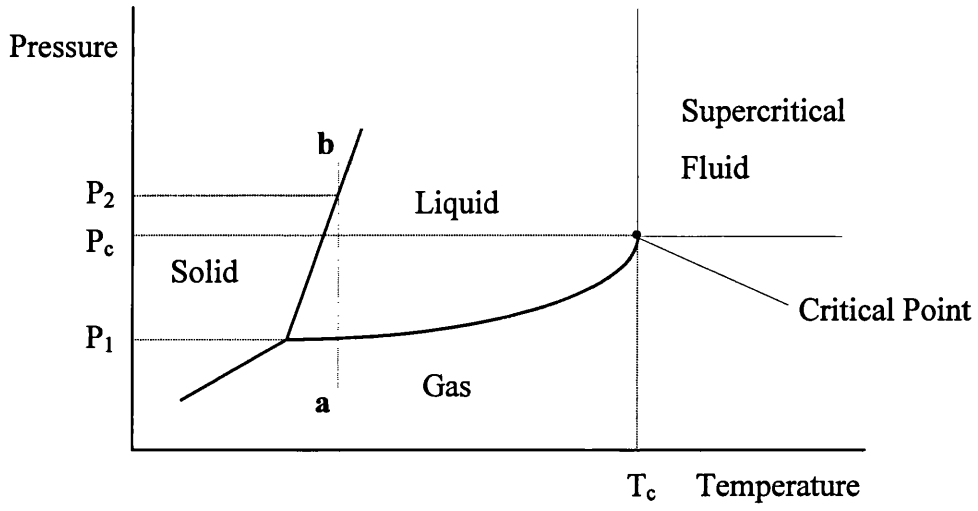



**Figure 2.1.** Phase Diagram for Carbon Dioxide (after Atkins, 1990)

Changes of state can also be achieved by varying the pressure, for example, if a gaseous sample of carbon dioxide at point **a** (Figure 2.1) is compressed to point **b**, at constant temperature, the sample will liquefy at pressure $P_1$ and solidify at pressure $P_2$.

The critical point of carbon dioxide is also shown on Figure 2.1. This corresponds to a critical temperature ($T_c$) of 31.1°C and a critical pressure ($P_c$) of 73.8 bar (McHugh and Krukonis, 1994). Above the critical temperature and pressure, the carbon dioxide is said to be in the supercritical state. In this state no phase change can occur; the pressure can be raised indefinitely, yet a liquid phase will not form.

The physical properties of supercritical fluids can be varied greatly by manipulating the temperature and pressure, but as a general rule they tend to be in-between those of a liquid and a gas. As an example, supercritical carbon dioxide at 200 bar has a diffusivity of $\sim 10^{-4} cm^2/s$. The diffusivity of carbon dioxide gas is $\sim 10^{-3}$ $cm^2/s$ and that of a typical hydrocarbon liquid is $\sim 10^{-5}$ $cm^2/s$ at standard temperature and pressure (McHugh and Krukonis, 1994). Viscosity follows a similar trend.

At sufficiently high pressure the density of a supercritical fluid is comparable to that of a liquid (e.g. the density of carbon dioxide at 600 bar and 50°C is 800 $kgm^{-3}$ (Vukalovich and Altunin, 1965)). This results in the solvent capacity of high pressure carbon dioxide being similar to that of a liquid.

The fact that the physical properties of supercritical fluids can be easily manipulated make them appear to be desirable solvents for solvent extraction processes, as discussed in Section 2.7.1. The high diffusivity and low viscosity of supercritical fluids when compared to liquids, together with zero surface tension, are advantageous in both solvent extraction and chromatography (Section 2.7.2).

## 2.3. History of Supercritical Fluids

It has been known for over 100 years (Andrews, 1875) that if a fluid is subjected to a temperature above its critical temperature it cannot be liquefied. Increasing the pressure of such a fluid will increase the density, but a liquid phase will not be formed. Fluids above their critical temperature and pressure are termed dense gases, or more commonly supercritical fluids.

Hannay and Hogarth (1880) discovered that the solubility of solids in supercritical fluids was very much higher than expected. In initial experiments they dissolved potassium iodide in ethanol and placed a small amount of this solution in a sealed glass tube. When this solution was heated to temperatures considerably higher than the critical temperature of ethanol only one vapour phase was visible. No precipitate of potassium iodide was seen as would be expected if it was not soluble in ethanol vapour.

In further experiments they constructed apparatus to allow solid potassium iodide to be contacted with supercritical ethanol and found that it dissolved. On releasing the pressure a precipitate of potassium iodide was formed (Hannay and Hogarth, 1880).

Villard (1898) dissolved a number of solids in supercritical fluids, notably bromine and iodine in supercritical oxygen and air. By observing changes in the colour intensity of the solutions he inferred that solubility was changing with pressure. This work led him to believe that the solvent power of a supercritical fluid was related to its density. He conducted his experiments at room temperature, and at pressures up to 300 atm, but did not measure the solubilities.

Little further work was done involving supercritical fluids until the 1940's when Diepen and Scheffer (1948) conducted studies on binary systems where the two components differed greatly in volatility. They observed that the solubility of naphthalene in supercritical ethylene was very much higher than expected and constructed apparatus to measure this solubility.

They contacted ethylene with excess naphthalene at the required temperature and pressure until equilibrium was reached. The supercritical solution formed was removed under constant pressure and cooled to crystallize the naphthalene and liquefy the ethylene. The solubility was calculated after measuring the mass of naphthalene and ethylene.

Diepen and Scheffer (1948) plotted solubility against pressure for naphthalene dissolved in supercritical ethylene at fixed temperatures, and showed that smooth lines could be drawn through the data points; deviation from these lines was slight. The authors took this to indicate that their results were accurate. In discussing the results it was noted that at lower temperatures the slope of the pressure versus concentration curve was small at pressures around 53 atm, i.e. a small increase in pressure led to a large increase in solubility. At 11°C, the critical temperature of the solution, a point of inflection occurred. At higher temperatures the curve was considerably smoother, indicating the sudden increase in solubility only occurred near the critical temperature.

Robin and Vodar (1953) attempted to interpret their own experimental data on the solubility of phenanthrene in supercritical fluids, as well as the results of Diepen and Scheffer (1948). They recognised that the higher than expected solubility of solids in the supercritical fluids meant that expressions such as Dalton's rules and Van-der-Waals's equation were not valid. They used the virial equation of state, limited to the second coefficient and considered only dilute solutions. They found reasonable agreement between the experimental results and the theory.

Tsekhanskaya *et al.* (1962) measured the solubility of diphenylamine and naphthalene in supercritical carbon dioxide as part of their work to investigate rates of diffusion in compressed gases. They used a static type of apparatus in which a compressed tablet of solute of known mass was placed in an equilibrium cell. The required amount of carbon dioxide was pumped into the cell and the system was allowed to reach equilibrium. The volume of carbon dioxide used was verified by releasing it into a calibrated glass vessel. The mass of solute which had been dissolved in the carbon dioxide was found by measuring the mass of the solute

remaining in the equilibrium cell. Errors were estimated using the method of least squares, and were found to be less than 5%.

A criticism which could be levelled at this work is that the pressure in the equilibrium cell was not measured directly. It was discovered that dissolving a solute in the supercritical carbon dioxide lowered the pressure, hence the pressure in the cell at equilibrium was lower than the experimental pressure. Tsekhanskaya *et al.* (1964) addressed this problem by repeating some of the earlier work with the same apparatus, but using repeated gas admission to ensure the equilibrium cell was at the correct experimental pressure. The solubility of naphthalene in supercritical ethylene was also studied using this method, and the results obtained were found to be in good agreement (within 2-4%) with those measured by Diepen and Scheffer (1948).

The work of Tsekhanskaya *et al.* (1964) is seen as the basis for measuring solubility. A number of later workers, including Kurnik *et al.* (1981) and Kramer and Thodos (1988), tested new apparatus by measuring the solubility of naphthalene in supercritical carbon dioxide and comparing the results with those of Tsekhanskaya *et al.* (1964).

## 2.4. Measuring Solubility in Supercritical Fluids

Since the early 1980's there has been considerable interest in using supercritical fluids in solvent extraction, supercritical fluid chromatography and as a reaction medium. As a result of this a large number of workers have measured the solubility of various solids and liquids in supercritical fluids. The methods used to measure solubility can be split into two categories; flow systems, where a continuous stream of supercritical solution is formed; and static systems, where the solution is formed in a closed, mixed vessel, and a sample is withdrawn for analysis. Flow systems are by far the more popular, and can be split up into groups depending on how the concentration of the supercritical solution is evaluated. Gravimetric, chromatographic, and spectrometric methods have all been used successfully.

### 2.4.1. Static Systems

The apparatus used by Diepen and Scheffer (1948) and Tsekhanskaya *et al.* (1962), as described in Section 2.3 are early examples of static systems. Both workers used gravimetric techniques to calculate the solubility.

Chrastil (1982) also used static apparatus to produce a saturated supercritical solution. The system was pressurized and stirred until equilibrium was reached and a measured volume of the solution was isolated under pressure in a pipette. The amount of solute present was found by dissolving it in a liquid solvent, making this up to a known volume, and using spectrophotometry, thin layer chromatography, or gas chromatography.

Yu *et al.* (1995) used a static system with a high pressure view cell to measure the solubility of polychlorinated biphenyls (PCBs) in supercritical carbon dioxide. The internal volume of the cell could be varied using a hydraulically driven piston. The experimental technique involved loading a known mass of PCB into the cell, before pumping a known amount of carbon dioxide in. The cell was heated to experimental temperature, and the contents stirred with a magnetic stirrer. The pressure was slowly increased by moving the piston while the contents of the cell were viewed using a camera and monitor. Solubilisation of the PCBs in the carbon dioxide was deemed to have occurred when the last particles of PCB disappeared, and only one phase was visible.

Repeat readings were taken by depressurising and repressurising the cell whilst observing the contents. Variations of less than 5% were noted. Yu *et al.* (1995) compared results obtained with those from other workers and found a good agreement at lower pressures. At higher pressures (up to 680 bar) however, differences of up to 9% were noted.

### 2.4.2. Flow Systems

#### 2.4.2.1. Gravimetric Analysis

Kurnik *et al.* (1981), Johnston and Eckert (1981), and Kramer and Thodos (1988) worked independently, but used similar flow-type experimental rigs to measure the solubility of substances such as naphthalene in supercritical carbon dioxide and ethylene. The apparatus used is shown, (Figure 2.2) and consists of a high pressure pump which compresses the gas from the supply cylinder. The compressed gas is heated before entering the equilibrium cell, where it contacts the test solid. The temperature is carefully controlled. On leaving the equilibrium cell the supercritical solution is throttled, and passes through a cold trap where the solid which was dissolved is collected. The mass of solid collected is found by accurately weighing the cold trap at the start and end of the experiment. The volume of gas used is found by passing it through a gas meter.

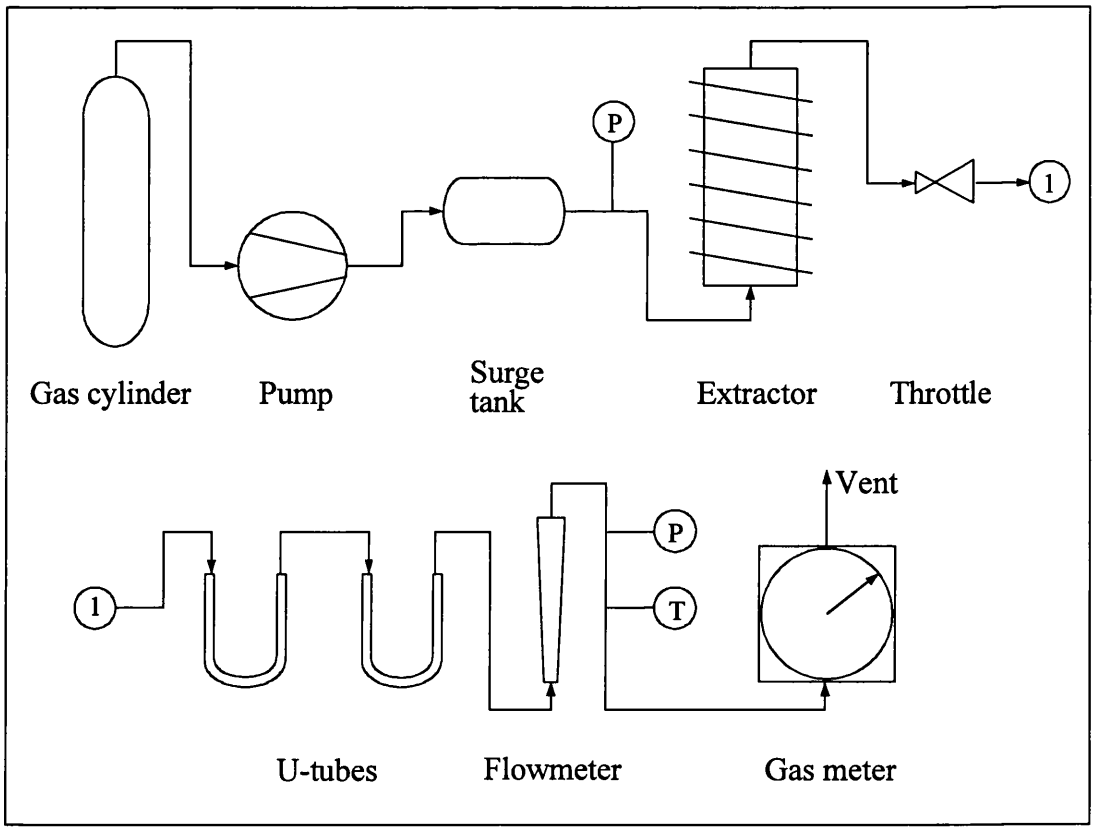



**Figure 2.2.** Experimental rig used by Kurnik *et a.l* (1981).

All these workers compared the results they obtained with those of Tsekhanskaya *et al.* (1964), and found deviations of less than 5% indicating their work was accurate.

A number of workers used flow systems similar to that of Kurnik *et al.* (1981) but with modifications to improve accuracy or ease of use. Iwai *et al.* (1989) used two equilibrium cells in series to ensure equilibrium was reached. The value of this is somewhat questionable, as Kurnik *et al.* (1981) conducted a series of experiments at different supercritical fluid flow rates. This had no effect on the solubility measured proving that equilibrium is quickly reached. They also varied the distribution of the test solid in their equilibrium cell and again this had no effect on the results obtained.

Madras *et al.* (1993) used a packed bed of activated carbon to adsorb the solute from the supercritical solution, rather than using a cold trap. The major advantage of this system was the solute was removed before the fluid was throttled down to atmospheric pressure. This avoided the problem of solute fouling the throttle valve. The amount of solute collected in the adsorption column was found gravimetrically. Madras *et al.* (1993) reported results within 1-2% of those of Tsekhanskaya *et al.* (1964).

Mendes *et al.* (1995) used two cold traps in series to ensure all the solute was collected. They noted that usually nothing was collected in the second trap indicating that one trap should be sufficient.

#### 2.4.2.2. Chromatographic Analysis

McHugh and Paulaitis (1980) used a flow system similar to that of Kurnik *et al.* (1981) but included a switching valve before the throttle valve, to allow a sample of the supercritical solution to be isolated. The volume of carbon dioxide in the sample loop was found by expanding it slowly across a valve, displacing water. The solute was washed out of the sample loop with a solvent, and the concentration determined using gas chromatography. The results obtained compared well (within 2-4%) to those of Tsekhanskaya *et al.* (1964).

#### 2.4.2.3. Spectrometric Analysis

Smith *et al.* (1987) adapted apparatus designed for supercritical fluid chromatography - mass spectrometry, as described by Smith and Udseth (1983) in order to measure solubility in supercritical fluids using very small volumes of materials. Their apparatus consisted of a high pressure pump to supply the supercritical fluid via an injector to a capillary. The capillary was situated in a constant temperature oven and the internal surface was coated with the solute under test. Equilibrium was reached in the capillary and the resulting supercritical solution was then fed into a mass spectrometer.

The major advantage of this system was that a number of results could be taken quickly by increasing the pressure stepwise from a selected starting point. A short wait between steps was needed to allow the system to reach equilibrium before the composition was measured. A complete pressure - solubility curve could be plotted from one experiment. The mass spectrometer was calibrated at the end of each series of runs, using a standard solution of the solute under test. The disadvantage of this technique was that it was limited to systems where the solubility was low as the amount of solute deposited on the capillary was low.

### 2.4.3. Co-solvents

Many workers who studied the solubility of solids in supercritical carbon dioxide found the solubilities measured were very low, even at high pressures. In an attempt to increase solubility they added small amounts of co-solvents (also called modifiers or entrainers) to the carbon dioxide. Among the first workers to report the effectiveness of entrainers were Kurnik and Reid (1982). They studied the solubility of solid mixtures in supercritical carbon dioxide and noted that the solubility of a solid in a multicomponent solute system was up to 300% greater than the solubility of the pure solid.

Workers who studied the effects of co-solvents used flow type experimental rigs as described above, with either gravimetric or chromatographic analysis. Two different

methods have been used to add the co-solvents to the system. The most straightforward involved using a cylinder containing carbon dioxide with a known amount of co-solvent to supply the rig. Cygnarowicz *et al.* (1990) used pre-prepared cylinders of carbon dioxide with known amounts of methanol, ethanol or methylene chloride added in their work measuring the solubility of β-carotene. Other workers (Ekart *et al.*, 1993; Ting *et al.*, 1993; Dobbs *et al.*, 1986) prepared their own mixtures by adding a known volume of carbon dioxide to a measured amount of co-solvent in a pressure vessel. This method gave the flexibility of being able to change the solvent composition from run to run, but made the experimental procedure more complex and time consuming.

The second method to add a co-solvent involved the use of an additional high pressure pump. This was used by Tavana *et al.* (1989), who used duplex metering pumps to supply known amounts of supercritical fluid and co-solvent to their rig. They included a pre-heater/mixer vessel prior to the equilibrium cell to ensure the two input streams were well mixed. Tavana *et al.* (1989) used a conventional cold trap to collect the solute dissolved, and followed this with a cryogenic trap, immersed in liquid nitrogen to remove the co-solvent from the carbon dioxide stream.

Considerable research by Dobbs and co-workers (Dobbs *et al.*, 1986; Dobbs *et al.*, 1987) was done on non-polar and polar co-solvents. In 1986 they investigated the effects of non-polar co-solvents, such as *n*-pentane and *n*-octane, added in small amounts (3-7%) to supercritical carbon dioxide on the solubility of phenanthrene and hexamethylbenzene. They noted the effect of the co-solvents was the same on both solutes, increasing the solubility by 100-300%. The work done in 1987 showed different results with polar co-solvents such as methanol and acetone. These enhanced the solubility of polar solutes (benzoic acid and 2-aminobenzoic) by up to 600%, yet had a small effect on non-polar hexamethylbenzene. Dobbs *et al.* (1987) concluded that while polar co-solvents can have a large effect on solubility, but only on certain polar solutes, non-polar co-solvents have a smaller effect on both polar and non-polar solutes.

More recently, Ekart *et al.*, (1993) used a chromatographic technique to investigate the interactions between a range of co-solvents and three supercritical fluids, carbon dioxide, ethane and fluoroform. They presented a large amount of data on these fluids, and discussed the effects of the different co-solvents in terms of polarity.

## 2.5. Predicting Solubility in Supercritical Fluids

Measuring the solubility of substances in supercritical fluids is time consuming and expensive, requiring specialist equipment. It quickly became clear to the early workers in the field of supercritical fluids that a method to accurately predict solubility would be a very useful tool, saving time and money. Diepen and Scheffer (1948) noted that expressions such as Dalton's rule were not in agreement with experimental data for supercritical solubility. Their results showed that the measured solubility of naphthalene in supercritical ethylene was 3 or 4 orders of magnitude greater than that calculated with Dalton's rule. Robin and Vodar (1953) also noted that traditional thermodynamic expressions including Daltons rules and Van-der-Waals equation of state were not in agreement with experimental data, but showed that the solubility of phenanthrene in a number of different gases could be correlated using the expression:

$$\log_{10} m = A + B\rho \qquad (2.1)$$

$m$ = solubility (weight basis)

$\rho$ = density of gas

$A$, $B$ = constants

Robin and Vodar (1953) then considered statistical thermodynamics, and used an equation of state limited to the 2$^{nd}$ virial coefficient in order to predict solubility. They found that this approach predicted solubilities of the correct order of magnitude, but was lacking in accuracy.

Tsekhanskaya *et al.* (1962) measured the solubility of diphenylamine and naphthalene in subcritical and supercritical carbon dioxide. They noted that a minimum solubility was seen at pressures a little lower than the critical pressure of carbon dioxide, and solubility increased rapidly as the pressure was increased above the critical value. They deduced that equation 2.1 could be used to correlate this data, but was only valid at pressures greater than the critical pressure of the gas.

More recent attempts to predict solubility in supercritical fluids has focused on the use of traditional thermodynamics, based on equality of fugacities:

$$f_i^s = f_i^{sol} \tag{2.2}$$

$f_i^s$ = fugacity of component i in solid phase

$f_i^{sol}$ = fugacity of component i in solution

From Prausnitz *et al.* (1986), the fugacity of a pure solid, component i, is given by:

$$f_i^s = P_{VPi}\Phi_i^s \exp\left[\int_{P_{VPi}}^{P} \frac{V_i^s}{RT} dP\right] \tag{2.3}$$

$P_{VPi}$ = Vapour pressure of solute

P = System pressure

$\Phi_i^s$ = Fugacity coefficient of solute

$V_i^s$ = Molar volume of solute

R = Gas constant

T = System temperature

For a solid, the molar volume is assumed to be independent of pressure, and hence the integral can be evaluated. $\Phi_i^s$ is assumed to be 1 at low solid vapour pressure. Therefore equation 2.3 becomes:

$$f_i^s = P_{VPi} \exp\left[\frac{V_i^s(P - P_{VPi})}{RT}\right] \tag{2.4}$$

From Prauznitz *et al.* (1986), the fugacity of a solid in solution is given by:

$$f_i^{sol} = y_i \Phi_i P \qquad (2.5)$$

$y_i$ = Mol fraction of solute (i) in solution

$\Phi_i$ = Fugacity coefficient of solute in solution

Equations 2.2-2.5 can be used to derive the following expression for the equilibrium mole fraction of solute dissolved in a high pressure gas:

$$y_i = \left(\frac{P_{VPi}}{P}\right)\left(\frac{1}{\Phi_i}\right)\exp\left[\frac{V_i^s}{RT}(P - P_{VPi})\right] \qquad (2.6)$$

While $P_{VPi}$ and $V_i^s$ data was available for common solutes, $\Phi_i$ was the only term that reflected the fact that the fluid phase was a mixture, and hence accurate estimates of this were required. $\Phi_i$ can be calculated using a mixture equation of state, for example the Redlich-Kwong equation of state (Redlich and Kwong, 1949). Modifications to this equation of state, for example by Soave (1972) and Peng and Robinson (1975), have been used to give greater accuracy.

## 2.6. Polymers and Supercritical Fluids

Supercritical fluids can have a range of effects on polymers, depending on the materials in question, and the temperature and pressure at which they are brought into contact. Ehrlich (1992) produced a review of the subject and noted that often supercritical fluid/polymer systems follow the behaviour shown in Figure 2.3.

At comparatively low pressures two phases would be formed, a polymer rich phase and a supercritical fluid rich phase. The polymer would swell and adsorb the supercritical fluid, and the supercritical fluid would dissolve some of the polymer to form a solution. From Figure 2.3, at a pressure of P, the supercritical fluid phase would contain the weight fraction of polymer, A, and the polymer rich phase would

have the weight fraction B. At sufficiently high pressure, the figure reaches a maximum, known as the upper critical solution pressure (UCSP). At pressures above this, the system will become completely miscible.

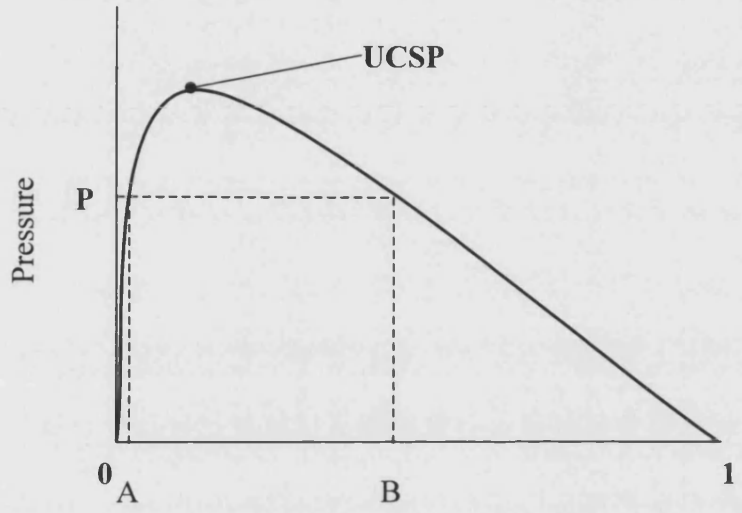



**Figure 2.3.** Solubility isotherm of a binary polymer-solvent mixture, with complete miscibility in the supercritical phase. From Ehrlich (1992).

The ability of many polymers to absorb subcritical and supercritical fluids and swell in their presence is a phenomenon which has been considered by a number of workers. Bonner (1977) considered the implications of gases being dissolved during polymer processing, and produced a review paper which concentrated mainly on the solubility of gases and supercritical fluids in molten polymers. McHugh and Krukonis (1994: 357-360) presented details of an experimental rig used to obtain sorption and swelling data for polymethylmethacrylate in the presence of supercritical carbon dioxide. They go on to discuss the formation of porous polymers using supercritical fluids.

Over the last 15 years there has been a growing interest in processing polymers using supercritical fluids, and in particular supercritical carbon dioxide. There are many examples in the literature of using supercritical fluids to purify polymers, either by

extracting residue monomers or by fractionating the polymers to give a number of cuts, each with a narrow range of molecular weights (Section 2.6.1). Research has also concentrated on enhanced oil recovery using supercritical fluids modified with polymers (Section 2.6.2) and pharmaceutical polymer processing with supercritical fluids (Section 2.6.3).

### 2.6.1. Solubility of Polymers

With the increased interest has come some published data on the solubilities of polymers in supercritical $CO_2$, together with accounts of methods used to obtain the data. Heller *et al.* (1985) used a static system to investigate the solubility of a range of polymers in both liquid and supercritical carbon dioxide. Their results are vague; solubilities are presented in the units grammes per litre, without stating whether the volume is that of compressed or atmospheric carbon dioxide, and each measurement taken at a different temperature and pressure. Among the most soluble of the polymers investigated were poly butene (atatic, MW 434), solubility = 8 g/l, and poly α decene (MW not stated), solubility = 10.5g/l.

Heller *et al.* (1985) concluded that both stereochemistry and molecular weight play an important part in the solubility of polymers in carbon dioxide. Atatic polymers, where the pendent groups are randomly arranged along the length of the polymer, tend to be amorphous. These have a higher solubility than isotatic examples of the same polymer, which tend to be crystalline, and have the pendent groups lined up on the same side of the polymer chain. Experiments comparing the solubility of the same polymer with different molecular weights showed the expected trend that solubility decreases with increasing molecular weight.

### 2.6.2. Enhanced Oil Recovery

At the temperatures and pressures typically found in oil reservoirs, (~100°C and 200 bar) carbon dioxide has been found to be a useful displacement agent in enhanced oil recovery operations. The main problem with carbon dioxide is that its viscosity is an

order of magnitude lower than that of crude oil. The higher mobility associated with this low viscosity severely reduces the efficiency of the process.

Heller *et al.* (1985) attempted to dissolve polymers in carbon dioxide in order to increase the viscosity. Their work involved measuring the solubility of a number of polymers in liquid and supercritical carbon dioxide at temperatures of 20-50°C and pressures up to 240 bar. They then used a modified falling cylinder in tube viscometer to measure the viscosities of these high pressure solutions. They found that poly(methyl oxirane) increased the viscosity of carbon dioxide by 1.25 times at 30°C and 164 bar, but decided this was not sufficient for enhanced oil recovery purposes. Further work in this field was done by Iezzi *et al.* (1989), who investigated the effects of surfactants, tri-n-butyltin fluoride, and semi-fluorinated alkanes on the viscosity of supercritical carbon dioxide. The semi-fluorinated alkanes showed the most promising results, as they formed gels in the carbon dioxide, but the increase in viscosity was not measured.

### 2.6.3. Pharmaceutical Polymer Processing

Tom and Debenedetti (1991a) measured the solubility of poly (L-lactic acid) (L-PLA) and poly (DL-lactic acid) (DL-PLA) in supercritical carbon dioxide with and without acetone as a co-solvent. They used a flow-type rig together with chromatographic analysis, similar to the equipment used by McHugh and Paulaitis (1980). They found that the solubility of L-PLA in supercritical carbon dioxide was closely related to the molecular mass of the polymer. When commercial L-PLA, which is polydisperse was loaded into the cell, the initial solubilities measured were ~0.1 wt % at 55°C and 250 bar. This was reduced to <0.03 wt% after a significant amount of carbon dioxide had been passed through the cell. Analysis of the extract from the cell showed that initially, low molecular weight L-PLA had been collected. The molecular weight of the extract increased as the solubility decreased proving that the solubility of a polymer in supercritical carbon dioxide is dependent on the molecular weight of the polymer. To verify this result, the residue remaining in the cell after a series of experiments was analysed. It was found that the average molecular mass of the

residue was significantly higher than that of the starting material. The results for DL-PLA followed the same trend.

The solubility of L-PLA and DL-PLA in supercritical carbon dioxide were both low and so Tom and Debenedetti (1991a) used acetone as a co-solvent. Acetone was selected as L-PLA and DL-PLA dissolve in it. They found an increase in solubility of 500% with 1% acetone added to the carbon dioxide.

## 2.7. Current Applications of Supercritical Fluids

Although the increased solvent capability of high pressure gases was first discovered over 100 years ago, it was not exploited commercially until 50 years after. Wilson *et al.* (1936) discussed a way to use near critical propane to remove asphalt from oil. The first commercial process to use a truly supercritical fluid was coffee decaffeination (Zosel, 1974; Roselius *et al.*, 1974). Currently the largest commercial use for supercritical fluids is in extraction. Supercritical fluids are also used as a reaction medium; the polymerization of ethylene takes place in supercritical ethylene. Analytical and semi-preparative supercritical fluid chromatography is used regularly in research laboratories. All of the above processes and the use of supercritical fluids to produce defined particles and films are still the subject of much research.

### 2.7.1. Supercritical Fluid Extraction

Supercritical fluids generally have physical properties such as viscosity and diffusivity somewhere between those of a gas and a liquid. One exception is density, which tends to be similar to that of a liquid, thus supercritical fluids have a high solvent capability. Randolph (1990) highlights these properties as desirable for solvent extraction. Villard (1898) first noted that the solvent capacity of a supercritical fluid can be varied by changing its density. Thus supercritical fluid extraction processes can be controlled by controlling the pressure, and hence the density of the process.

The 1970's technology can be gauged from a review paper by Eggers (1978), where the design of large scale plant for supercritical extraction is discussed. A straightforward process is described, where a stream of supercritical fluid is contacted with the material to be extracted in an extraction vessel. The supercritical solution formed is then throttled down. The extract is collected in a demixing vessel and the solvent is recycled via pumps and heaters. By manipulating the pressure in the extraction and demixing vessels the quality and quantity of the extract can be controlled.

More complex processes have since been developed. Destraction is the name given to the process described by Warzinski and Ruether (1984). Extraction takes place as described above and the resulting solution is then fed to a fractionating column. The temperature and/or pressure gradient within the column cause the extract to be separated into a number of components. The supercritical solvent may be recovered from the top of the column, and recycled as before.

The growing importance of supercritical fluid extraction is evident from the number of publications, conferences and symposia on the subject. A specialist journal, "The Journal of Supercritical Fluids" is published quarterly; the International Society for the Advancement of Supercritical Fluids holds an annual symposium, and a detailed text book has been written, and is now in its second edition (McHugh and Krukonis, 1994).

The most commercially important supercritical fluid extraction process is the decaffeination of coffee, and a number of patents have been issued relating to this. The first was by Zosel (1974), and involved circulating wet supercritical carbon dioxide through a bed of moistened green coffee beans. The carbon dioxide containing caffeine was passed through a water pool, where the caffeine was extracted. This process removed half the caffeine from the coffee beans. The water in the pool was changed three times to allow sufficient caffeine to be removed. Six months later Roselius *et al.* (1974) patented a complex process which involved extracting coffee oil from roasted coffee beans with dry supercritical carbon dioxide. Caffeine was then extracted from the beans with wet supercritical carbon dioxide. A

coffee extract was produced from the decaffeinated beans which was mixed with the coffee oil to produce a product which tasted acceptable. More recent methods have also been patented, some involving the use of adsorbents to remove caffeine from supercritical solutions (Zosel, 1981).

Considerable research has been conducted using supercritical fluids, especially carbon dioxide, to extract edible oils and flavour and odour components from foods. Examples include extracting oils from soya beans, sunflower seeds, and fish extracts, (Friedrich, 1984) and extracting the aroma components from hops, lemons, herbs and spices (Gaspar *et al.,* 1997). Traditionally food components are extracted using organic solvents such as hexane and heptane. There is however a move to reduce the use of organic solvents for environmental and safety reasons and carbon dioxide is a clean and safe replacement. Traditional processes tend to run at higher temperatures which can have an adverse effect on the quality of the extracts, especially delicate taste components. The critical temperature of carbon dioxide is 31°C hence supercritical extraction processes use lower temperatures which do not degrade extracts.

Other commercially viable uses for supercritical fluid extraction include oil up-grading and deasphalting, removing organics from water, regenerating activated carbon, and extracting useful components from coal.

The major disadvantage concerning supercritical extraction is the high pressures that are needed in order for the extracts to dissolve. High pressure equipment is expensive to buy and run, and the safety issues of high pressure work need to be considered. In the 1970's supercritical extraction was hailed as the major way forward for difficult separations. The high costs involved, along with other technical problems have reduced this excitement. However, with environmental legislation becoming tighter, clean processes including supercritical extraction will continue to be developed.

### 2.7.2. Supercritical Fluid Chromatography

Supercritical fluids were first used as mobile phases for chromatography in the 1960's. Giddings *et al.* (1968) published a detailed paper discussing high pressure gas chromatography and pointed out three advantages over liquid chromatography, the only alternative for chromatography of macromolecules.

- The solvent power of the supercritical fluid depends on pressure and hence can be easily manipulated. The solvent composition must be changed in liquid chromatography in order to affect the same control.

- The high diffusivity and low viscosity of supercritical fluids means that supercritical fluid chromatography is up to ten times as fast as liquid chromatography.

- The sensitivity of supercritical fluid chromatography is far higher than that of liquid chromatography.

Disadvantages of supercritical fluid chromatography stem from the cost and complexity of the high pressure equipment and problems with detection at high pressures. In order to overcome the detection problems relating to high pressure solutions Giddings *et al.* (1968) depressurized the supercritical solution as it left the chromatography column, producing a dilute gas. This was then fed into a flame ionisation unit for detection purposes. The authors claimed this was successful although they conceded they had problems with the macromolecules condensing out before the flame ionisation unit, leading to erroneous results.

More recently Smith *et al.* (1984) used a mass spectrometer as the detector with supercritical fluid chromatography. In their system the supercritical fluid from the chromatography column was fed directly into the mass spectrometer thus giving a high degree of accuracy. The detection limits were found to be as low as 0.1 pg.

Smith *et al.* (1984) demonstrated supercritical fluid chromatography as a powerful analytical tool. Campbell and Lee (1985) showed that supercritical fluid chromatography could also be used on a semi-preparative scale by using it to fractionate coal tar.

### 2.7.3. Chemical Reactions in Supercritical Fluids

Krase and Lawrence (1946) patented the first chemical process to take place in a supercritical medium; the polymerization of ethylene in supercritical ethylene. The process was actually developed by ICI in the 1930's. The use of supercritical fluids as reaction media has been discussed by McHugh and Krukonis (1994: 311-332). They noted that the supercritical fluid may participate in the reaction or may act as a solvent for the reactants, catalyst or products, or all three. The advantages of using supercritical fluids over traditional reaction media are:

- Clean supercritical fluids such as carbon dioxide can often be used to replace hydrocarbon reaction media.

- Certain compounds have been found which can only be made in a supercritical reaction medium.

- Supercritical reaction media are highly tuneable. By changing the pressure and hence the density, the selectivity of reactions can often be changed.

- Heterogeneous catalysts can be regenerated in the presence of a supercritical fluid, leading to increased productivity (Tiltscher *et al.,* 1984).

- The solvent characteristics of supercritical fluids can often be exploited when separating the product from the reactants, catalyst and by-products, reducing down stream processing costs.

The major commercial application of a supercritical reaction medium has been described by Boysen (1981) as the high pressure production of polyethylene. This

takes place at pressures of 1500-3000 atm, and temperatures up to 300°C in either a stirred autoclave or a tubular reactor. In both cases the ethylene together with a chain transfer agent and an initiator are pressurized and fed into the reaction vessel. In the autoclave reactor the product is obtained by controlled discharge of the polyethylene / ethylene mixture from the bottom of the autoclave. In the tubular system a pulsating valve discharges the mixture to a lower pressure. The conversion in both cases is 15-40 %, and the remaining ethylene is separated from the product in a number of stages by lowering the pressure. The unreacted ethylene is recycled while the polyethylene is formed into pellets or powder to be sold. The reaction which takes place is a free radical chain reaction, hence initiators such as oxygen or peroxide are required. The quality of the product is controlled by the type and ratio of chain transfer agents used; alkenes and olefins are examples.

Current research work in this area is focusing on making new compounds in supercritical media which could not otherwise be made, and replacing environmentally harmful media with substances such as supercritical carbon dioxide. The work by Banister *et al.* (1993) on preparative scale organometallic chemistry covers both of these points.

### 2.7.4. Production of Defined Powers and Particles

Defined powders are often required for pharmaceutical applications. Current methods of producing powders, such as controlled crystallisation from a liquid solvent, grinding, crushing, and milling have considerable disadvantages (Tom & Debenedetti, 1991b). All processes tend to produce particles with a broad size distribution which often need to be separated and graded before they can be used. Controlled crystallisation can result in product loss, and traces of solvent remaining in the powder produced. The mechanical methods are unsuitable for heat sensitive or waxy solids.

Hannay & Hogarth (1880) were the first workers to notice that if a supercritical solution is cooled, or the pressure lowered, the solute comes out of solution and forms a powder (provided it is in the solid phase). This phenomenon was the subject

of a patent by Smith (1986), and was further investigated by Matson *et al.* (1987). These workers developed a technique called Rapid Expansion of Supercritical Solutions, or RESS, which involved expanding a supercritical solution under controlled conditions through a defined nozzle or orifice. The expansion caused a large drop in the dissolving power of the solvent hence the solute precipitated out of solution. By varying the conditions of the supercritical solution, such as temperature, pressure and concentration of solute, different products were formed.

Work investigating RESS was carried out on a number of systems by Matson *et al.* (1987), including silica dioxide ($SiO_2$) in supercritical water, and polystyrene in supercritical pentane. For the $SiO_2$-water system, spheres of $SiO_2$ with a small size distribution were formed. By changing the concentration of $SiO_2$ in the solution prior to expansion, the size of the spheres produced could be varied, with more concentrated solutions producing larger particles. The authors also demonstrated that this technique can be used to deposit films by producing a film >1μm thick of $SiO_2$.

Other workers in this field have also investigated RESS. Petersen *et al.* (1987) formed fibres with a range of polymers using supercritical pentane. They noted that the diameters of the fibres produced were fairly uniform, and investigated the effect of the nozzle diameter on the diameter of the fibres produced. Tom and Debenedetti (1991a) used RESS to produce microparticles of bioerodible polymers, as discussed in Section 2.7.5.

Gallagher-Wetmore *et al.* (1994) used a similar method to RESS in order to produce defined particles. They referred to their technique as Supercritical Fluid Nucleation. Carbon dioxide was used as the supercritical fluid, with prednisolone and closely related compounds as the solutes.

A different method to produce defined particles using supercritical carbon dioxide called Gas Anti Solvent (GAS) recrystallisation was developed by Gallagher *et al.* (1989). This involved dissolving the solid in question in a traditional solvent, usually a hydrocarbon, before adding supercritical carbon dioxide. The carbon dioxide

dissolved in the solution causing a decrease in density and creating a supersaturated solution. At this point the solid would be precipitated.

Gallagher *et al.* (1989) developed this technique for producing fine particles of explosives which are otherwise difficult to comminute. They successfully prepared small particles of nitroguanidine using dimethyl formamide as the hydrocarbon solvent. They noted that adding the carbon dioxide rapidly (over a period of 5 seconds) gave rise to very small particles (~5μm) whereas adding the carbon dioxide slowly (5 minutes) led to the formation of much larger "snowballs" of loosely held together rods.

Further work by Gallagher *et al.* (1992) used the same technique to produce particles of cyclotrimethylenetrinitramine, a high explosive, using acetone or cyclohexanone as the solvent. Their aim was to make particles free from the voids and cavities produced when the particles are formed by solvent evaporation or liquid anti-solvent techniques.

More recently, Ruchatz *et al.* (1997) used the same system, which they called Aerosol Solvent Extraction System to produce microparticles of poly-L-lactide, from a methylene chloride solution. Supercritical carbon dioxide at 40°C and 90 bar was used as the anti-solvent, and they investigated the levels of methylene chloride which was left in the microparticles following their production.

Advantages of this system include; it is suitable for use with solids which are insoluble in supercritical carbon dioxide and it gives a pure product with very little solvent contamination, due to the fact that the solvent used is completely miscible with, and is removed by the supercritical carbon dioxide. The obvious disadvantage is that a hydrocarbon solvent is still used and hence the environmental problems associated with this remain.

York and Hanna (1996) developed a process called Solution Enhanced Dispersing by Supercritical Fluids (SEDS) which was similar to GAS recrystallisation in that a conventional solution was mixed with supercritical carbon dioxide to cause

precipitation of the solute. The novel part of the SEDS process was the use of a coaxial nozzle used to introduce the supercritical carbon dioxide and the organic solution into the pressure vessel. As the two streams impinge on each other in the nozzle considerable turbulence is caused leading to the dispersion of the precipitated solute. By accurately controlling all the process variables (flow rates of carbon dioxide and solution, temperature and pressure) they were able to influence the characteristics of the particles produced more accurately than was possible with GAS recrystallisation. They demonstrated the effectiveness of the SEDS process by preparing samples of Salmeterol Xinafoate, an anti-asthma drug, with particle sizes in the range 1-10 μm. They found that the Salmeterol Xinafoate particles produced were free from retained solvent and uncharged. The shapes of the particles produced depended on the hydrocarbon solvent used to dissolve the drug initially, with thin blade like structures being formed with ethanol, and agglomerations of flat particles formed using acetone.

### 2.7.5. Producing Controlled Release Drugs with Supercritical Fluids

For a drug to be effective in the body it must be at the correct concentration in the blood stream. Injecting drugs or taking them orally usually results in an initial high concentration of the drug in the blood stream, which decreases to a very low level until the next dose is administered. It is advantageous to be able to administer drugs in such a way that they are slowly made available in the body and so the concentration remains constant. A review by Juni and Nakano (1987) discusses controlled release dosage forms based on poly (L-lactic acid) (L-PLA), poly (DL-lactic acid) (DL-PLA) or poly(glycolic acid) (PGA). These polymers are slowly hydrolysed to lactic acid or glycolic acid, which are harmless, within the body. A wide range of dosage forms where a drug is incorporated into a polymer matrix have been studied. These include plates, beads and rods for implanting, and ground particles and microspheres for injection. It was found possible to control the rate of release in the range of dosage forms by using mixtures of L-PLA, DL-PLA and PGA.

Tom and Debendetti (1991a) conducted a range of nucleation experiments to produce microspheres of L-PLA using supercritical carbon dioxide with and without acetone

as a co-solvent. They varied both the extraction and expansion temperature and pressure in an attempt to produce regular microspheres of diameter less than 50μm. The molecular weight of the L-PLA extracted varied as discussed in Section 2.4 and this was taken into account when conducting the experiments. The supercritical solution formed was expanded through a laser drilled orifice, of diameter 25-30μm, and deposited on a glass slide.

They found that when extracting higher molecular weight L-PLA, microspheres of the desired size were obtained using 1% acetone co-solvent, at extraction conditions of 55°C and 240 bar and expansion conditions of 15-37°C and 10-15 bar. The hydrolysis rate of the L-PLA microspheres was found to be similar to that of commercial L-PLA powder. They conducted further experiments using DL-PLA and PGA and found the solubility of these were similar to that of L-PLA.

Work by Larson and King (1986) showed that the anti-cholesterol drug Lovastatin was soluble in supercritical carbon dioxide (0.04 wt% at 40°C and 345 bar) and in supercritical carbon dioxide with 5% methanol (0.4 wt% at the same conditions). They went on to show that precipitating the Lovastatin from supercritical solution gave needles shaped particles in the size range 10-50μm.

Tom *et al.* (1993) attempted to use the RESS technique to produce controlled release polymer drug microspheres. They expanded a mixed solution of L-PLA and Lovastatin in supercritical carbon dioxide across a laser drilled orifice and obtained microspheres of L-PLA embedded with needles of Lovastatin. By changing conditions in the extraction and expansion stages the size and morphology of the particles could be changed. Tom *et al.* (1993) thought that on expanding the supercritical solution the lovastatin precipitated out first, forming needles which act as nucleation sites for the L-PLA. This resulted in the coating effect seen.

### 2.7.6. Painting Using Supercritical Fluids

As described in Section 2.1, there is a current move to reduce VOC emissions to atmosphere. Car paints tend to be applied using a mixture of organic solvents. Volatile solvents are used to lower the viscosity of the paint so it can atomize as it is sprayed from the gun. These flash off quickly and less volatile solvents are needed to allow the paint to flow together to form a film on the car. Busby *et al.* (1990) developed a method of replacing the volatile solvents with supercritical carbon dioxide. The new system can use the same airless spray equipment that is in regular use, as the temperature and pressure used remain at ~50°C and ~100 bar respectively. The spray characteristics of the supercritical sprayed paint are superior to that of a conventional airless spray, with fine droplet size and a feathered spray giving a uniform coating thickness. This method has been tested successfully with a wide range of paint types, and may have many applications. The only disadvantage is that not all the organic solvents are replaced by carbon dioxide, however a 70% reduction in VOC emissions is claimed.

The application of tablet coatings is obviously similar to applying spray paint to a surface. The technology described above shows that there is already a precedent for the use of supercritical carbon dioxide as a substantial part of a solvent blend to dissolve and apply coating materials. However, as pharmaceutical coating materials differ from paint there is a need to investigate this area fully.

# Chapter 3. Experimental Rig, Methods and Materials

## 3.1. Design and Construction of Experimental Rig

### 3.1.1. Aim

The rig was designed to measure the solubility of a range of tablet coating polymers in supercritical carbon dioxide, at temperatures up to 200°C, and pressures up to 600 bar.

### 3.1.2. Method

The solubility of solids in supercritical fluids has been measured by a number of different methods, as discussed in Section 2.4. A method similar to that of Kurnik *et al.* (1981) was chosen for the following reasons:

- It has been used successfully in a number of applications.
- The method is straightforward.
- It does not require any complex and expensive equipment such as a gas chromatograph or mass spectrometer as other methods.

The method involves passing a steady flow of dry supercritical carbon dioxide through a packed bed of polymer at experimental temperature and pressure. The length of the packed bed is such that the fluid leaving is a saturated solution of polymer in carbon dioxide. This solution is throttled down to atmospheric pressure and passes through a cold trap. The polymer precipitates out and is retained in the trap. The carbon dioxide vents via a dry gas meter. Having measured the mass of polymer, and the volume of carbon dioxide the solubility can be calculated. A flow diagram of the rig is shown in Figure 3.1.

### 3.1.3. Equipment Used

Carbon Dioxide. Carbon dioxide (99.8%), was supplied by BOC Limited, Surrey, U.K., in liquid withdrawal cylinders filled to 60 bar at 20°C. No regulator was required as the carbon dioxide was pumped to a higher pressure than the cylinder.

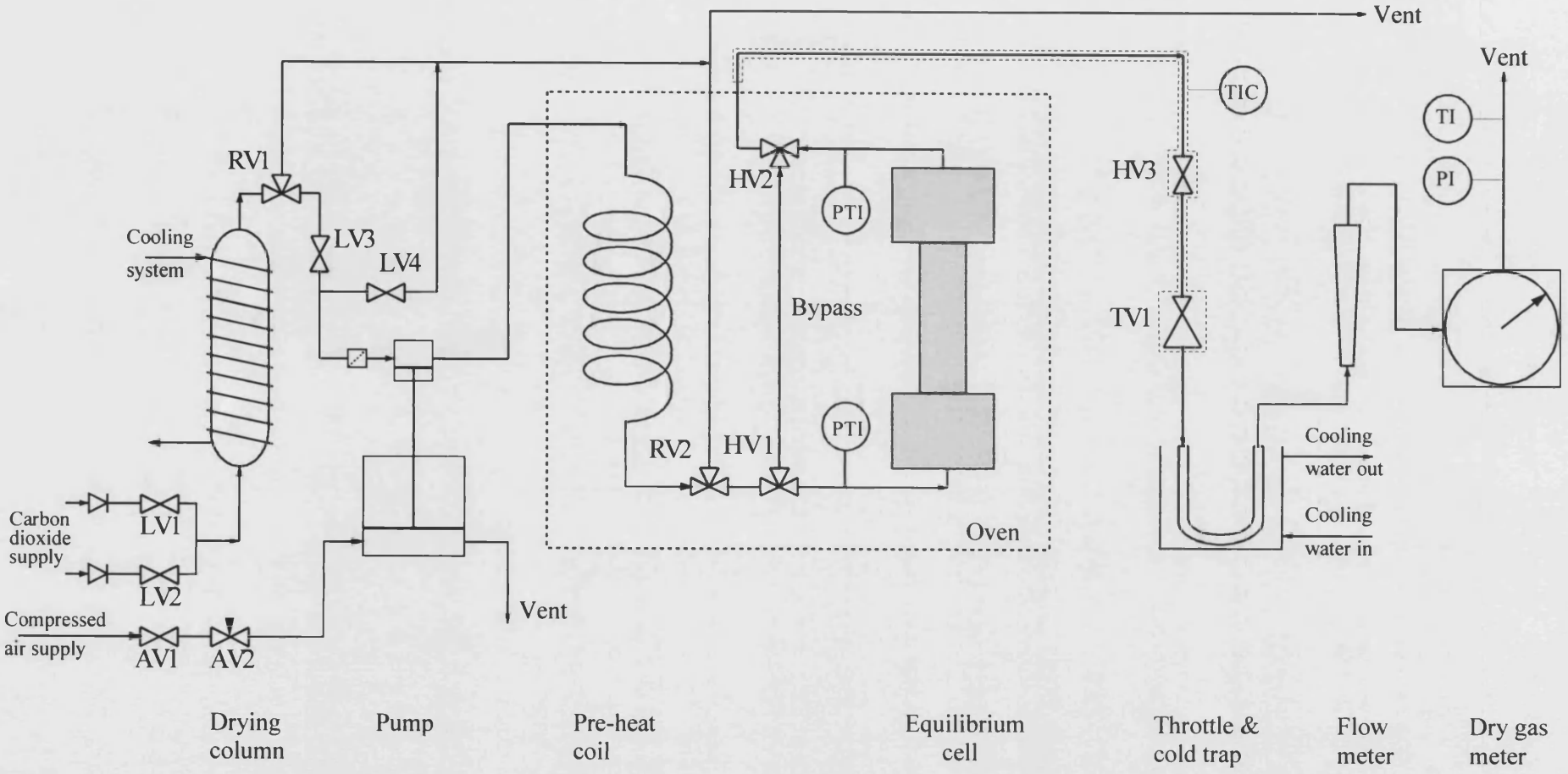



**Figure 3.1.** Flow diagram of supercritical solubility rig

Drying Column. A sample cylinder (Swagelok Company, Ohio, U.S.A.), with an internal volume of 3785 $cm^3$ was used as a drying column. This was filled with a suitable adsorbent (5Å molecular sieves, Aldrich Chemical Company, Poole, U.K). The adsorbent was regenerated regularly by heating to 300°C in the presence of nitrogen.

Cooling System. In order for the pump to operate satisfactorily, the carbon dioxide feed had to be in the liquid phase. As carbon dioxide is very volatile, it had a tendency to vaporise in the drying column, or in the pump head. To overcome this problem antifreeze solution was passed through silicone rubber tubes wrapped round the drying column and pump head to cool them. A refrigeration unit, (Grant, Cambridge, U.K.) and stirred water bath (Haake, Berlin, Germany) were used to circulate the antifreeze solution at approximately -4°C.

Relief Valve. (RV1) A proportional relief valve (Swagelok Company, Ohio, U.S.A.) was used to protect the low pressure side of the rig from over pressurising. This was set to lift at 90 bar, 30 bar higher than the operating pressure of this part of the rig.

Pump. A compressed air driven pump (Teledyne, Ohio, U.S.A.) was used to supply the carbon dioxide at experimental pressures up to 600 bar. This pump had a mechanical separation between the head and the air driven side to prevent contamination of the carbon dioxide with oil. The carbon dioxide pressure was controlled by manipulating the inlet air using a pressure regulator.

High Pressure Tubing and Fittings. The tubing (0.08" wall thickness, 1/4" outside diameter, 316 stainless steel) was supplied by Southampton Tube Sales, Southampton, U.K. This had a pressure rating in excess of 20,000 psi (1380 bar), at 200°C. The fittings used were either from the Sno-Trik range (Swagelok Company, Ohio, U.S.A.), or from Autoclave Engineers, Pennsylvania, U.S.A., and had a pressure rating of 60,000 psi (4140 bar).

Preheat Coil. This was formed by bending a 3 m length of high pressure tubing to form a coil 200 mm in diameter and was connected to the rig using Sno-Trik unions.

Relief Valve (RV2) In order to protect the high pressure side of the rig, a relief valve, set to lift at 10,000 psi (690 bar) was included upstream of the equilibrium cell (Autoclave Engineers, Pennsylvania, U.S.A.). This vented outside via a 28mm copper line.

Equilibrium Cell. This was a cylindrical vessel, of internal length 35 cm, diameter 1.8 cm and volume 89 $cm^3$. It was designed in-house and constructed from 316 stainless steel. Details of the design are given in Section 3.1.4.

Valves. All high pressure valves used were manufactured by Autoclave Engineers, Pennsylvania, USA. These had a pressure rating of 30,000 psi (2070 bar). A micrometering valve from the same company was used as the throttle to allow accurate flow control.

Oven. In order to carry out studies at a range of temperatures, the equilibrium cell together with the preheat coil were situated in an oven, made to BS 2648 (Gallenkamp Leicester, U.K.). A proportional, integral and derivative (PID) controller maintained the set point temperature to ± 0.1°C. In order to protect the pressure cell from over heating, the oven was also equipped with an independent thermostat, which was set to operate should the temperature exceed the set point by 20°C.

Trace Heating. The length of tubing leaving the oven and the valves V3 and V4 were heated to experimental temperature to prevent the solute from precipitating before the throttle valve. The thermostatically controlled trace heating equipment was made in-house and was set to the experimental temperature.

Pressure and Temperature Measurement. Dual pressure and temperature transducers were included before and after the equilibrium cell (Paine, Washington, U.S.A.). These incorporated a spiral wound strain gauge to measure the pressure, and a platinum resistance temperature device (RTD) to measure temperature. The digital display unit was made in-house, and gave a direct reading of temperature and pressure.

Cold Trap. This was made in-house and consisted of a glass U-tube placed in a vessel filled with water and maintained at approximately 15°C. A number of U-tubes were made from 18mm soda glass tubing, and were as light as possible to reduce errors when measuring the mass of solid collected: they weighed approximately 60g each. They are shown in Figure 3.2, and have a threaded joint to connect with the tube coming from the throttle valve. The ground glass joint was sealed with a PTFE sleeve rather than silicone grease, which would have affected the weight. A chamber was included before the ground glass joint which holds a plug of glass wool to act as a filter to trap entrained particles.

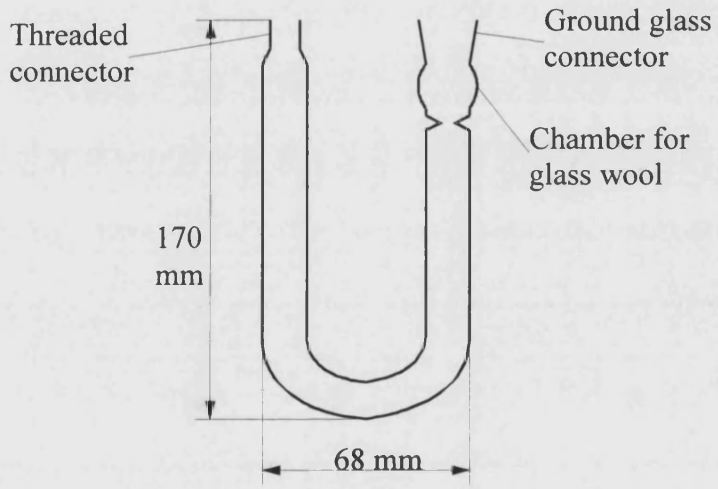



**Figure 3.2.** U-tube for cold trap

Gas Meter. A dry gas meter (Fisher, Leicester, U.K.) measured the volume of carbon dioxide gas used in each experiment. Accuracy was ± 0.2 $dm^3$ at standard temperature and pressure. The use of a wet gas meter was considered as these are more accurate but they are unable to handle the large volumes of gas required.

### 3.1.4. Design of Equilibrium Cell

The pressure cell was designed in-house to reduce cost and made by SmithKline Beecham. It was designed as a thick walled pressure vessel based on the information given by Juvinal (1983), Shigley (1986) and BS 5500. To satisfy pressure regulations the design was checked by National Vulcan Engineering Insurance Group Ltd. (Manchester, U.K.), and the cell was hydrostatically tested to 1250 bar by

Baskerville Ltd. (Manchester, U.K.).

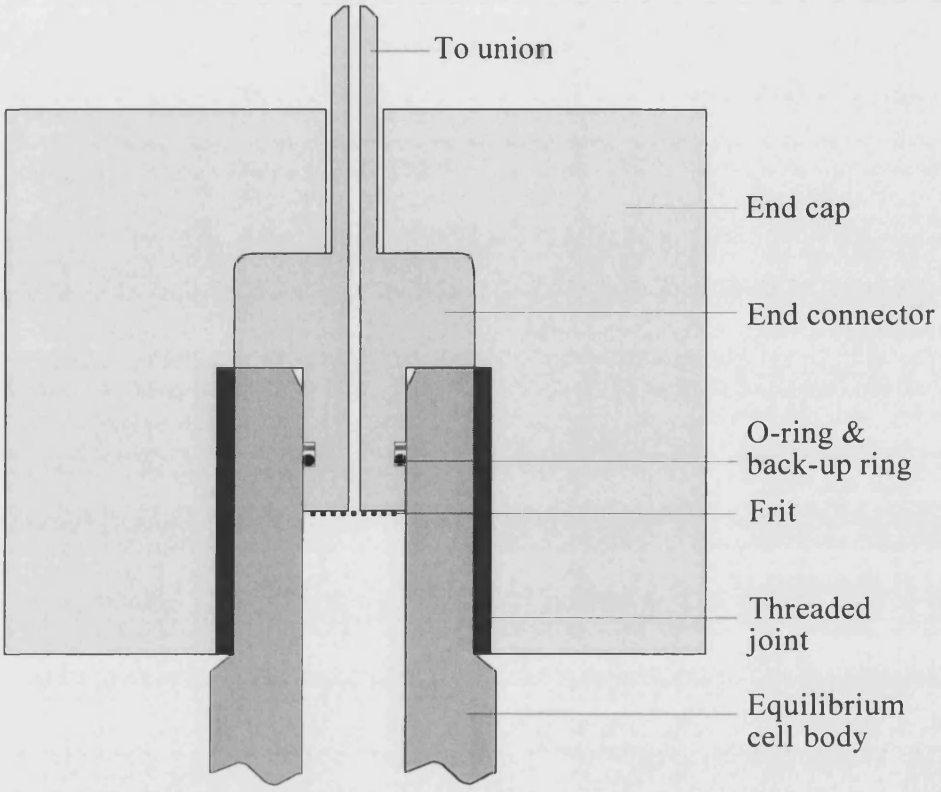



**Figure 3.3.** Equilibrium cell end fittings.

The cell was machined from 2" (50 mm) 316 stainless steel bar, to give an internal diameter of 18 mm. The internal length was 350 mm, giving a total volume of 89,000 $mm^3$ (89 $cm^3$). The cell end fittings are shown in Figure 3.3. The cell was attached to the rig at each end by end connectors machined to take standard Autoclave Engineers unions. The end connectors incorporated fine stainless steel frits, welded in place, to prevent carry over of particles, and were held in place with threaded end caps. Viton rubber O-rings (Precision Polymer Engineering, Blackburn, UK) were used to give a pressure tight seal between the cell and the end connectors, in conjunction with PTFE backup rings.

Detailed calculations were conducted on all components of the equilibrium cell. For straightforward parts of the design such as the wall thickness, and the thread load stress, conventional hand calculations were used. Complex components including the end caps and end connectors were modelled using "Ansys", a finite element analysis package. Manufacturing drawings of the different components were

produced including all dimensions and tolerances required. This information is reproduced in appendix A.

## 3.2. Experimental Procedure

The principles on which the rig operates are described in Chapter 2. In order to ensure accurate and repeatable results the following steps were performed when measuring the solubility of a chosen polymer in supercritical carbon dioxide:

a) Turn on the cooling unit and ensure the pump head is cold (less than 3°C) before carrying out step c. (The time taken for the pump head to get cold was such that the cooler unit was left on continuously.)

b) Check that the equilibrium cell and end connectors are clean and dry and renew the O-ring seals on the end connectors. Load the cell by first pouring in approximately 5 $cm^3$ of 1.5mm balottini to act as a support for the polymer and a distributor for the carbon dioxide. Then load with the polymer under test, mixed with 1.5mm balottini if required to bulk out polymers only available in small quantities. Include a plug of glass wool at the top to prevent the carry over of entrained powder. Install the cell in the oven and tighten the connectors. Check the rig visually to ensure that the bypass circuit is closed and the circuit through the equilibrium cell open (valves V1 and V2). Switch on the pressure and temperature meter.

c) Check the system for leaks. Close valves V3 and V4 and turn on the carbon dioxide and air supplies. Slowly increase the pressure in the rig by increasing the air supply to the pump, and check for leaks around all fittings using a liquid leak detector (soap solution). Continue until full operating pressure (600 bar) is reached. At the end of the check, the rig should be depressurized by turning off the air and carbon dioxide supplies and opening valves V3 and V4. If a leak is detected during the test, depressurize the rig as described before correcting the problem.

d) Turn the oven on, setting the desired temperature. The secondary thermostat

should be set 20°C above the desired temperature. Set the trace heating to the test temperature. Leave the rig to heat up fully (approximately one hour).

e) Close valves V3 and V4. Turn the carbon dioxide and air supplies on and slowly increase the air supply to the pump until the test pressure is reached (between 100 and 600 bar).

f) Ensure a U-tube is correctly situated in the cold trap before opening valve V3, and using the micrometering valve V4 to control the flow of carbon dioxide at the desired rate (approximately 2 litres/minute).

g) Maintain the flow of carbon dioxide until 20 litres have been passed (10 minutes). This ensures a saturated supercritical solution is reaching the throttle valve. Close valve V3.

h) Insert a clean U-tube, which has been weighed to ± 0.1mg, into the cold trap. Note the reading on the gas meter.

i) Run the system for a predetermined length of time checking the pressure and temperature regularly and adjusting if necessary. Measure and note the pressure and temperature at the gas meter. The length of a run depends on the solubility of the material under test, as sufficient solid needs to be collected so it can be weighed accurately. For the most soluble materials, 40 litres of carbon dioxide, at room temperature and pressure, was collected (20 minutes), for the least soluble, 240 litres (2 hours) was required.

j) To stop the experiment close valve V3. Remove the U-tube from the cold trap and weigh to ± 0.1mg. Note the reading on the gas meter.

k) The solubility was calculated, as described below. The solubility data for all the polymers studied have been presented in the units wt%, calculated as described below. The data for naphthalene has been presented in the units mol% to enable direct comparison with the data of Tsekhanskaya *et al.* (1964).

Experimental Data:

Volume of carbon dioxide, V = 41.6 litres
= 0.0416 $m^3$

Temperature of carbon dioxide at gas meter, $T_c$ = 20°C

Pressure of carbon dioxide at gas meter, $P_c$ = 1 bara

Initial mass of U-tube, $M_a$ = 61.4415 g

Final mass of U-tube, $M_f$ = 63.9439 g

Calculate mass of carbon dioxide used:

From Vukalovich and Altunin (1965):

Density, ρ, of carbon dioxide at 20°C and 1 bar = 1.815 kg $m^{-3}$

Therefore mass of carbon dioxide used, $M_{CO_2}$ = ρ * V
= 1.815 * 0.0416
= 0.0755 kg, = 75.5 g.

Calculate mass of solute collected:

Mass of solute collected, $M_s$ = $M_f - M_a$
= 63.9439 - 61.4415
= 2.5024 g

The mass fraction of solute in solution, M

$$= \frac{M_s}{M_s + M_{CO2}}$$

$$= \frac{2.5024}{2.5024 + 75.5}$$

= 0.032g/g
= **3.2 wt%**

l) Following a series of experiments with one polymer it was necessary to clean the rig. It was found that material was often carried out of the equilibrium cell and deposited in the lines running both to and from the cell. This had to be removed as it would have had an effect on the measurements of the next material to be studied. The equilibrium cell had been designed to be easily dismantled, and was cleaned with acetone in which all the polymers studied

were soluble. The rest of the rig was cleaned by pumping acetone through it using the pump installed. Care was taken not to heat the rig during this procedure as acetone is flammable. Valves HV3 and TV1 were kept open to prevent a build up of pressure. Residual acetone was removed by blowing compressed air through the rig.

## 3.3. Commissioning and Testing the Rig.

This was done in two parts, a control test and solubility tests. The rotameter was also calibrated at this stage.

### 3.3.1. Calibrating the Rotameter

As the rotameter used was designed for measuring the flow rate of air at high pressure it was recalibrated for carbon dioxide at atmospheric pressure before any experiments were carried out. This was done by allowing carbon dioxide to flow at a fixed rate for a measured period of time. The volume of carbon dioxide passed was measured using the gas meter, and hence the flow rate calculated. This was done for 3 different flow rates over the full scale of the rotameter. This data was plotted on a graph and a linear relationship between flow rate and rotameter reading was seen. It was shown that the rotameter could be used with acceptable accuracy over the range 1.5 – 5 l/min.

### 3.3.2. Control Tests

In these tests the rig was run as described in Section 3.2, but with no polymer loaded into the cell. This was to ensure that any change in the mass of the U-tube occurred only because of test solute precipitating out. It was possible that impurities which may have been present in the carbon dioxide, balottini or glass wool could be carried through the rig and be deposited in the U-tube, leading to errors in the mass of solute measured.

A slight change of mass (around 5 mg) was observed on the first occasion this test

was carried out, and a fine brown powder was deposited in the U-tube. This was thought to be zeolite powder, carried over from the drying column, and so a 0.5 μm filter (Swagelok Company, Ohio, U.S.A.) was installed after the drying column, and before the pump. Subsequent control tests showed changes in mass of less than 1 mg, and this was considered acceptable.

### 3.3.3. Solubility Tests

The rig was verified by measuring the solubility of naphthalene in supercritical carbon dioxide. Naphthalene was selected as the naphthalene-carbon dioxide system has been extensively studied by a number of different workers. Teskhanskaya *et al.* (1964) measured the solubility of naphthalene in supercritical carbon dioxide at conditions up to 55°C and 320 atm. This work has become a standard and was used by Kurnik *et al.* (1981) and Johnston and Eckert (1981) in their work.

**Table 3.1.** Solubility of naphthalene in supercritical carbon dioxide.

| Temperature (°C) | Pressure (bar) | Solubility (mol%) | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | Average | Teskhanskaya *et al.* (1964) |
| 45 | 100 | 0.012 | 0.011 | 0.012 | 0.006 |
| | 150 | 0.019 | 0.018 | 0.019 | 0.019 |
| | 200 | 0.024 | 0.024 | 0.024 | 0.024 |
| 55 | 100 | 0.004 | 0.003 | 0.003 | 0.003 |
| | 150 | 0.025 | 0.026 | 0.025 | 0.026 |
| | 200 | 0.038 | 0.039 | 0.039 | 0.04 |

The testing was carried out using crystalline naphthalene GPR (99%), supplied by BDH, Poole, U.K. Temperatures of 45 and 55°C, and pressures of 100, 150 and 200 bar were used, and each experiment was repeated at least twice to check reproducibility of results. The results obtained, shown in Table 3.1 and Figure 3.4, are in close agreement with those of Teskhanskaya *et al.* (1964). This proves that the rig operates satisfactorily and gives reproducible and accurate results.

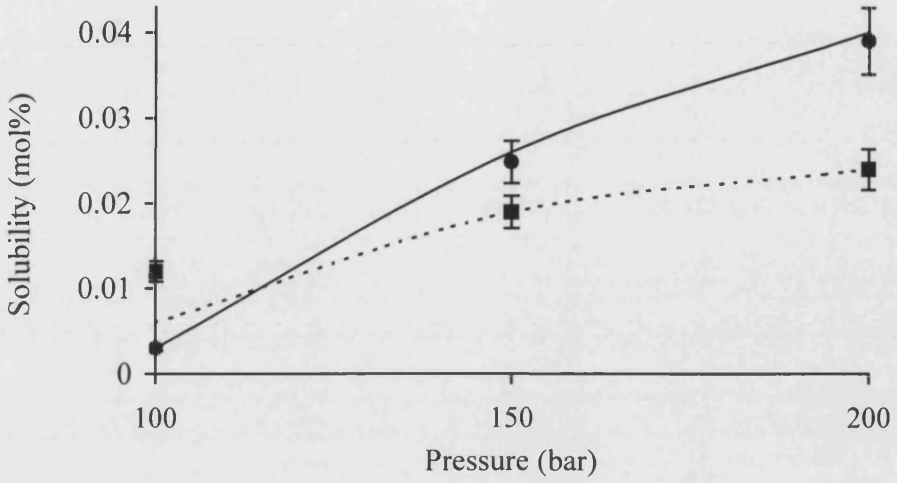



**Figure 3.4.** Solubility of naphthalene in supercritical carbon dioxide:
● this work, 55°C; ——— Teskhanskaya *et al.* (1964), 55°C;
■ this work, 45°C; - - - - - - Teskhanskaya *et al.* (1964), 45°C.

This testing allowed two questions regarding accuracy to be addressed:

a) Was equilibrium reached in the cell?
b) Was all the solute recovered in the cold trap?

a) Was equilibrium reached in the cell?

Solubility measurements relied on the carbon dioxide leaving the cell being in equilibrium with the test solid packed into the cell. Reports from other workers (Kurnik *et al.*, 1981) suggest that equilibrium is reached very quickly, as is expected due to the high diffusivity of supercritical carbon dioxide. In order to reach equilibrium the residence time of the carbon dioxide in the cell must be sufficiently long. A series of experiments at the same temperature and pressure, but at different carbon dioxide flow rates (hence residence times) were conducted with naphthalene as the solute. It can be seen from Table 3.2 that the solubility measured was the same at flow rates of 2, 3, 4 and 5 litres/minute of carbon dioxide at room temperature and pressure. From this it was decided that equilibrium was always reached in the cell. It was not possible, with the equipment available, to increase the flow rate beyond this. All experiments were run at approximately 2 l/min, to be

certain that equilibrium was being reached.

**Table 3.2.** Solubility of naphthalene measured at 55°C, 150 bar and different carbon dioxide flow rates.

| Flow rate of $CO_2$ (l/min) | Solubility of naphthalene (mol%) |
|---|---|
| 2 | 0.0252 |
| 3 | 0.0248 |
| 4 | 0.0256 |
| 5 | 0.0249 |

b) Was all the solute recovered in the cold trap?

There are two areas to consider here: (i) fine particles of solid could be carried right through the cold trap by the flow of carbon dioxide; (ii) solid could precipitate out in the throttle valve and not reach the cold trap.

In considering the first point, Mendes *et al.* (1995) used two cold traps in series to ensure all the solute was collected, but noted that usually nothing was deposited in the second trap. For this work, a plug of glass wool was inserted in the end of the U-tube to trap entrained particles. This was found to be successful with naphthalene, the most soluble material considered, as no deposits were seen in the fitting at the top of the U-tube, or in the rotameter which was situated immediately after the cold trap.

The second point is more complex and a number of workers using flow-type systems to measure solubility in supercritical fluids have reported methods to prevent solid from precipitating out in the throttle valve.

Yau and Tsai (1992), Mendes *et al.* (1995), and Kramer and Thodos (1988) all heated the throttle valve to temperatures higher than the melting point of the solid under test. This prevented the throttle valve from fouling, as any solute precipitated would be in the liquid phase and would flow into the cold trap. This method was considered in the present design, and trace heating was included on the throttle valve,

however two further problems were envisaged:

I. This work involves polymers which do not have a fixed melting point, rather they tend to soften gradually forming a very viscous liquid when heated above their glass transition temperatures. This is likely to increase fouling of the throttle valve.

II. The hydrocarbon polymers may degrade at higher temperatures.

Iwai *et al.* (1991) included a carbon dioxide bypass in their apparatus which allowed high pressure carbon dioxide to pass through the throttle valve without first passing through the equilibrium cell. This was used at the end of each experiment and effectively removed solute from the valve and into the cold trap. Figure 3.1 shows that a carbon dioxide bypass was included in the current design, controlled by valves V1 and V2, but with naphthalene this was not required.

Richter and Sovova (1993) considered the design of the throttle valve in more detail. They heated it, as discussed above, and also ensured that the path to be taken by the expanded gas was as short and direct as possible. The same considerations have been made in the present design; the U-tube is directly below the throttle valve, and the two are joined by tubing only 5cm in length. This design has proved to be successful in avoiding these problems.

## 3.4. Reproducibility and Errors

Care was taken to ensure all solubilities measured were as accurate as possible, subject to the limitations of the equipment used. There were a number of areas where errors could have been introduced, and these are discussed below. The maximum error in the solubility measurements was ± 10%.

### 3.4.1. Solute Collection

The U-tubes, used as cold traps were weighed on a four figure balance to ± 0.1mg at the start and end of each experiment, and the difference was taken as the mass of

solute which had been dissolved. This should give an overall error of ± 0.2mg in the mass of solute collected. There were other factors however which may have affected the weight of the U-tubes, and precautions were taken to overcome these. As noted previously, the ground glass joint on the U-tubes was sealed with a PTFE sleeve, rather than silicon grease, to avoid leaving slightly different masses of grease on the joint each time it was broken. It is well known that glassware in the laboratory can pick up water from the atmosphere, and this can have an effect on the mass when measured to this accuracy. Further, during the course of each experiment, the U-tube was placed in a container of distilled water, maintained at approximately 15°C. It is good practice to dry glassware in an oven at a temperature greater than 100°C, and then allow it to cool in a dessicator prior to weighing. Due to the heat sensitive nature of the polymers used during this work, it was not possible to heat the U-tubes in this way, and an alternative method was used.

Prior to weighing at the beginning and end of each experiment the U-tubes were washed with distilled water and dried using filtered and oil free compressed air. They were handled with lint free lens tissue to prevent grease from fingers adhering to them. In performing the control tests it was shown that the change in mass of a U-tube during a blank run (no test material in the equilibrium cell) was less than 1mg. It was therefore assumed that the mass of material collected in subsequent runs was measured to an accuracy of ± 1 mg. As at least 50 mg of solute was collected in the cold trap during any experiment, the maximum error in weighing was 2%.

### 3.4.2. Carbon Dioxide Measurement

The volume of carbon dioxide used for each experiment was measured using a dry gas meter which had an accuracy of ± 0.2 l. This was calibrated by the manufacturer and was used as received. All experiments were run for sufficient length of time to allow at least 40 l of carbon dioxide, at atmospheric temperature and pressure, to pass through the rig, and hence the volume used was known to an accuracy of 0.5%. The temperature and pressure of the carbon dioxide was measured as it entered the gas meter, using an alcohol thermometer and a mercury manometer, therefore the mass used could be calculated accurately, without introducing further significant error.

### 3.4.3. Temperature and Pressure Measurement

As can be seen in Figure 3.1, the temperature and pressure were measured at the entrance and the exit of the equilibrium cell using dual temperature and pressure transducers as described in Section 3.1.3. The transducers used platinum RTDs to measure temperature, and these were accurate to ± 0.1°C. They had been calibrated by the manufacturer over the temperature range 24-177°C. During the course of each experiment both temperatures were recorded. These were generally within 0.2°C of each other, and were never more than 0.5°C different.

The transducers used thermally compensated, spiral wound strain gauges in order to measure pressure. These were calibrated by the manufacturer over the pressure range 0-1000 bar, for temperatures in the range of 24-177°C. The maximum reported error was ± 0.25 % of full scale reading, or ± 2.5 bar. A larger error in measuring the pressure came from the type of pump used. The piston pump was operated so as to control the pressure in the rig at the desired level. Due to the action of the reciprocating piston, the pressure cycled by as much as ± 20 bar at a nominal rig pressure of 600 bar. The cycling was less at lower pressures, ± 5 bar at a rig pressure of 100 bar. This gave rise to a large error, up to 7.5%, at low pressures. At the higher pressures, 300-600 bar, used for most of the solubility experiments the error in pressure measurement and control was approximately 5%.

### 3.4.4. Repetition of Experiments

All experiments were performed twice as a minimum, to ensure results were repeatable. On a number of occasions, observations suggested an experiment had not run accurately. In section 4.5, the carry over of swollen polymer which was not thought to be dissolved in supercritical carbon dioxide is described. When observations such as these were made, the run was disregarded and repeated. Provided the two runs carried out were within 10 % of each other, they were accepted, averaged, and presented in the results. If this was not the case, the reasons why were investigated, and the experiment was repeated until two consecutive solubilities within 10 % of each other were measured.

### 3.4.5. Sources of Error

There were a number of reasons why experimental results may have been erroneously high or low. The most common cause of low solubilities being measured was the solution leaving the equilibrium cell was not saturated with solute, as there was too little solute present. This took place with the more soluble materials considered, and occurred because most of the solute had been removed during earlier runs. It was straightforward to remedy, by reloading the equilibrium cell, removing the more soluble material as described below, and repeating the erroneous measurements. Another problem which was thought to lead to low solubilities being measured was material precipitating out in the body of the throttle valve or the tube below it, and not being carried into the cold trap by the flow of carbon dioxide. If this happened, it could lead to an erroneously high reading during the subsequent experiment, should the built up material be dislodged, and fall into the cold trap. If this was thought to be happening, the temperature of the throttle valve was increased, in order to melt the polymer, and prevent it from adhering. High solubilities may have been measured due to material sticking in the throttle valve from a previous run, as described above, or because of swollen polymer, not thought to be dissolved in supercritical carbon dioxide, being carried over into the cold trap.

## 3.5. Modifications Required

While conducting the experimental work it became apparent that some modifications were required, both to the experimental procedure when measuring the solubilities of polymers, and to the rig itself in order to work with a liquid solute.

### 3.5.1. Modifications to Experimental Procedure

It has been noted in the literature (Tom and Debenedetti, 1991a) that the solubility of a polymer is related to its molecular weight, with solubility decreasing as the molecular weight increases. It has been stated by the manufacturers of some of the polymers used that the materials that they supply have an average molecular weight as stated, but consist of a polydisperse mixture. Further, polymers often contain

some unreacted monomer material of very low molecular weight. It was noted, on measuring the solubility of a polymer in supercritical carbon dioxide, that an initial peak in solubility was measured, signifying a component of high solubility. The measured solubility then reduced and plateaued after two to three experiments. The initial high solubilities were thought to be due to the removal of the most soluble, unreacted monomer. Once this was stripped from the cell, the measured solubility was then that of the polymer with the stated molecular weight, and the results were repeatable. Table 3.3 shows the solubilities measured initially for Poly (DL-lactide), MW 2,000 which illustrates this point.

**Table 3.3.** Initial solubilities measured for poly (DL-lactide) MW 2,000 in supercritical carbon dioxide.

| Run N° | Temperature (°C) | Pressure (bar) | Solubility measured (wt%) |
|---|---|---|---|
| 1 | 55 | 600 | 1.744 |
| 2 | 55 | 600 | 1.637 |
| 3 | 55 | 600 | 1.357 |
| 4 | 55 | 600 | 1.092 |
| 5 | 55 | 600 | 1.095 |

To avoid errors in measuring the solubility of polymers the following procedure was adopted and employed each time the equilibrium cell was loaded with fresh polymer. An experiment was carried out as described in Section 3.2. The highest pressure possible (600 bar) was used as it is known that solubility always increases with pressure, and the aim of this experiment was to strip out the more soluble components as efficiently as possible. The solubility was calculated and the same experiment repeated. This was continued until repeatable results were obtained.

### 3.5.2. Modifications to Experimental Rig

During the course of the experimental work it was decided to measure the solubility of a liquid in supercritical carbon dioxide. This presented some problems as the equilibrium cell had been designed to accept solid materials only. It was not feasible

to pour the test liquid into the cell, as it could only be filled after being removed from the oven, when both the top and bottom fittings were open. To overcome this problem, four stainless steel sample holders, each 40 mm long, were fabricated from ½" tubing. These were held together vertically with stainless steel wire, and could be easily slid down into the cell.

When conducting an experiment, each sample holder was filled approximately three quarters full with the liquid under test. A plug of glass wool was then placed in each holder to act as a wick and hence increase the area available for supercritical fluid / liquid contact. This was to ensure the supercritical carbon dioxide was at equilibrium with the liquid as it left the cell. The experiment could then be carried out as detailed earlier.

## 3.6. Experimental Programme

Initially a series of short experiments was carried out on a wide range of pharmaceutical excipients. These included the inexpensive and widely used hydroxypropylmethylcellulose, (HPMC), the enteric coating material Eudragit® RL100, and some little used materials with the potential to be successful controlled release coatings, poly (DL-lactide), poly (DL-lactide-co-glycolide), and poly-β-hydroxybuteric acid.

These preliminary experiments were carried out as described in Section 3.2, and the details of the materials used are given below. As this was a screening exercise the solubilities were measured at only one set of conditions. The results have been tabulated.

Materials were selected for more detailed study based on the preliminary results obtained. This work involved conducting a series of solubility experiments on each material at a range of temperatures and pressures; typically temperatures of 35-55°C and pressures of 300-600 bar were used. In some cases the limited availability of materials or experimental problems meant fewer experiments were conducted than

was desired. The results of this phase of work have been presented as both isotherms, and isobars in the following chapter. This allows the effect of both temperature and pressure on the solubility of the polymers to be considered in detail.

### 3.6.1. Materials Used

The pharmaceutical excipients studied are listed below, together with their characteristics and manufacturers or suppliers.

**Hydroxypropylmethylcellulose** USP (HPMC), of viscosity 6cP was manufactured by the Shin-Etsu Chemical Co., Tokyo, Japan. This is a water soluble polymer, widely used for film coating in the pharmaceutical industry.

**Eudragit® RL100** (Poly (ethyl acrylate, methyl methacrylate, trimethyl ammonioethyl methacrylate chloride) 1:2:0.2), was manufactured by Röhm Pharma, Darmstadt, Germany. Eudragit polymers are widely used for enteric and control release coatings. Some types are soluble in water, or can be applied as a suspension in water. Other types, especially the more useful ones require hydrocarbon solvents such as acetone or ethanol.

**Resomers.®** These are a range of polyesters based on poly lactide and poly glycolide, manufactured by Boehringer Ingelheim, Germany. They are available in a range in molecular weights and also as co-polymer mixtures. Resomers are known as resorbable materials because, while they are not soluble in water, they have the property of slowly degrading within the body (or in the environment) to give lactic acid or glycolic acid. This degradation time depends on the type of resomer, and the conditions it is exposed to, and can be anything from weeks to a year. All the resomers studied are soluble in hydrocarbon solvents including dichloromethane, acetone and tetrahydrofuran, and are amorphous polymers with glass transition temperatures in the range 5-60°C. Resomers are currently used for wound closures, surgical implants, and drug carriers and have potential for use in controlled release applications. The following resomers have been studied:

- R104H Poly (DL-lactide) of molecular weight 2,000
- R202H Poly (DL-lactide) of molecular weight 9,000
- RG502, Poly (DL-lactide-co-glycolide) 50:50 of molecular weight 3,000.
- RG502H Poly (DL-lactide-co-glycolide), with hydrophilic end groups, 50:50 of molecular weight 3,000.

**Poly (DL-lactide),** of molecular weight 90,000-120,000, was supplied by the Sigma Chemical Co., Poole, England.

**Poly (DL-lactide-co-glycolide)** 50:50, of molecular weight 50,000-75,000 was supplied by the Sigma Chemical Co., Poole, England.

**Poly-β-hydroxybutyric acid,** of molecular weight 535,000 was supplied by the Sigma Chemical Co., Poole, England.

## 3.7. Investigating Materials Formed

During the experiments to measure solubilities in supercritical fluids it was observed that the nature of the material collected in the cold trap varied depending on the polymer used, and to a lesser extent the temperature and pressure of the experiment. It was further noticed that the polymer in the equilibrium cell often underwent a physical change during the course of a series of solubility experiments. These observations were investigated more thoroughly.

### 3.7.1. Materials Collected in the Cold Trap

Observations were made at the end of each experiment with regard to the nature of the material collected in the cold trap. Where a fine powder was collected in sufficient quantities, the size, and size distribution of these particles was measured using a Mastersizer, (Malvern Instruments, UK). The particles were removed from the trap after it had been weighed by tapping it to dislodge those adhering to the walls of the tube, or trapped in the glass wool plug. They were poured into a clean

plastic bag which was gassed with dry nitrogen to eliminate water vapour. This was done as poly (DL-lactide) was known to be unstable, and liable to degrade in the presence of water. The samples were sealed and stored in a refrigerator until required.

To measure particle sizes, the Mastersizer requires them to be suspended in a suitable liquid. A laser beam is then shone through the suspension, and each particle causes the light to be scattered at an angle that is inversely proportional to its size. The scatered light is collected by a detector and analysis of the diffraction pattern enables the size distribution of the particles in the sample to be calculated.

The particles were suspended in distilled water for these tests. While it was noted above that the materials in question will degrade in the presence of water, this process takes a considerable length of time, i.e. weeks to months. It was assumed that no degradation would take place during the time taken to measure particle sizes, approximately 15 minutes.

### 3.7.2. Changes to Materials in the Equilibrium Cell

At the end of the series of experiments measuring the solubility of Eudragit RL 100 in supercritical carbon dioxide, it was noted that the polymer in the equilibrium cell had changed its physical form. In order to investigate this more thoroughly, a short series of experiments was carried out at different conditions as described below.

The equilibrium cell was refilled with polymer as described in Section 3.2. It was reinstalled in the rig, which was then brought up to experimental temperature. Care was taken to ensure the fittings were fully tightened as the pressure test described in Section 3.2 was not carried out. This was because it was required to measure the length of time the polymer was exposed to carbon dioxide at experimental pressure, and in conducting a pressure test this would have been difficult to ascertain. The rig was quickly brought up to experimental pressure, and the throttle valve opened to give a carbon dioxide flow of approximately 2 l/min at room temperature and pressure, thus mimicking the solubility experiments as far as possible. The rig was left to run at these conditions for a predetermined time, and observations were made

of any material deposited in the cold trap.

The rig was then depressurized by turning off the carbon dioxide supply and the pump. The throttle valve was gradually opened to give a steady carbon dioxide flow of 2 l/min, hence reduce the time taken to depressurize the rig. Once the equilibrium cell had cooled, it was taken out of the rig, and the polymer removed. When the polymer had swollen in the cell, it was necessary to hammer or drill it out.

# Chapter 4. Results

In conducting the experimental work it was decided to screen a range of pharmaceutical polymers, from the widely used hydroxypropylmethylcellulose to the more exotic and little used poly lactide and glycolide. This screening work was carried out at 600 bar, the highest pressure possible with the equipment available, as it is known from the literature that solubility always increases with increasing pressure. These preliminary results have been presented in tabular form.

As a result of this screening it was decided to concentrate on poly (DL-lactide), poly (DL-lactide-co-glycolide), and Eudragit® RL100. Lactic acid, the precursor to poly (DL-lactide), has also been studied in detail. The results for these materials are presented in the form of solubility isotherms and isobars. A summary table, Table 4.4, has been included at the end of this chapter, giving all the solubility data generated for these materials.

## 4.1. Preliminary Results.

Initially the polymers selected were screened by measuring their solubility in supercritical carbon dioxide at a pressure of 600 bar, and a temperature of 55-65°C. For poly-β-hydroxybutyric acid, the temperature was varied between 35 and 65°C as zero solubility was measured first time. These results are shown in Table 4.1. As noted in Section 3.4 the maximum error in the solubilities measured was ±10%.

**Table 4.1.** Solubility of miscellaneous materials in carbon dioxide

| Material | Molecular Weight | Temp (°C) | Pressure (bar) | Solubility (wt%) |
|---|---|---|---|---|
| HPMC | | 60 | 600 | 0.008 |
| Eudragit® RL100 | >100,000 | 60 | 600 | 0.019 |
| Poly (DL-lactide) | 105,000 | 55 | 600 | 0.014 |
| Poly (DL-lactide-co-glycolide) | 62,000 | 65 | 600 | 0.002 |
| Poly-β-hydroxybutyric acid | 535,000 | 35-65 | 600 | Insoluble |

The solubility of hydroxypropylmethylcellulose (HPMC) at 60°C and 600 bar was measured as 0.008 wt%, which is very low. It was decided to concentrate on some of the more "exotic" coating polymers, which are under used due to problems with their processing. The solubility of both Eudragit® RL100 and poly (DL-lactide) were around twice that of HPMC, and so these were studied in more detail. It was interesting to note that the solubility of poly (DL-lactide-co-glycolide) was an order of magnitude less than that of poly (DL-lactide), even though the molecular weight was significantly lower. This observation was investigated more thoroughly, as described in Section 4.3.

Poly-β-hydroxybutyric acid (PHB) was completely insoluble. There was no visible deposit formed in the cold trap at any of the temperatures tested (35, 45, 55, and 65°C), and 600 bar, and there was no significant change in mass. Hence this material was not studied any further.

## 4.2. Poly (DL-lactide)

The solubilities of poly (DL-lactide), of different molecular weights are presented in Figure 4.1 to Figure 4.4. The solubility isotherm of the lower molecular weight polymer, Resomer R104H (MW 2,000) is shown in Figure 4.1, and the isobar in Figure 4.2.

It is seen that the effect of pressure on the system is straightforward, with an increase in pressure leading to an increase in solubility. This is true for all temperatures studied, but is more obvious at the highest temperature than the lowest one. At 55°C, an increase in pressure from 300 to 600 bar gives rise to an increase in solubility of 0.9 wt%, whereas at 35°C, the same 300 bar pressure increase leads to only a 0.434 wt% increase. The effect of temperature is more complex; at 300 bar it is seen that the solubility is effectively independent of temperature, within the range of temperatures studied. At higher pressures however, temperature has an effect on the solubility of poly (DL-lactide), MW 2,000, in carbon dioxide. This can be seen more clearly from the isobars plotted in Figure 4.2.

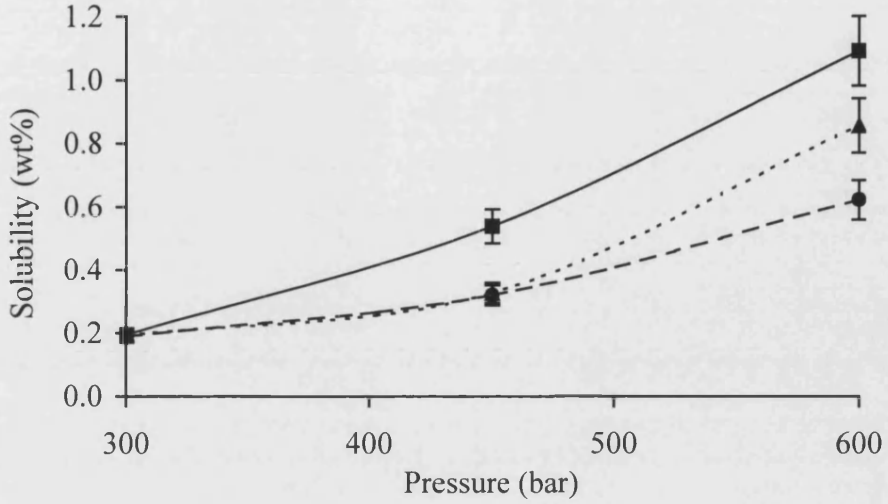



**Figure 4.1.** Solubility isotherms for poly (DL-lactide), MW = 2,000 in carbon dioxide at temperatures:

—■— 55°C, - - ▲ - - 45°C, — ● — - 35°C

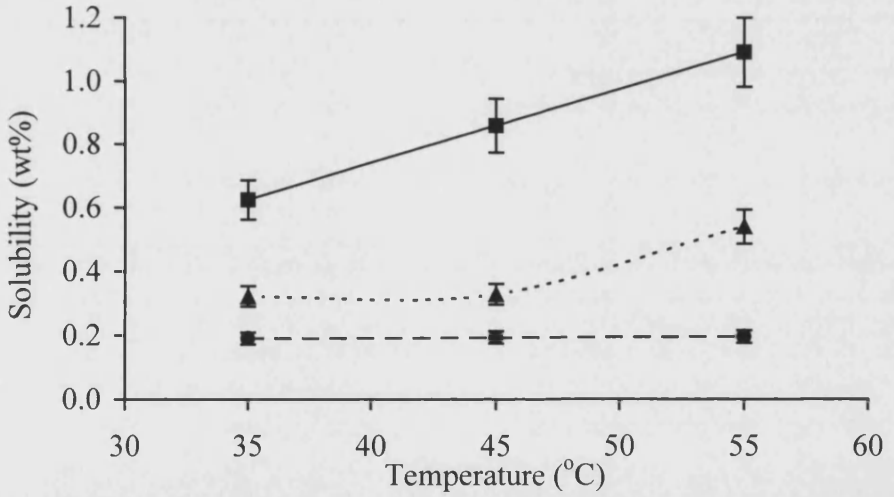



**Figure 4.2.** Solubility isobars for poly (DL-lactide), MW = 2,000 in carbon dioxide at pressures:

—■— 600 bar, - - ▲ - - 450 bar, — ● — - 300 bar

It is seen from Figure 4.2 that at the higher pressure (600 bar) the effect of varying the temperature on the solubilites measured was significantly greater than at lower pressures, particularly 300 bar where there was virtually no increase in solubility as the temperature increased. The increase in solubility on raising the temperature from

35-55°C was negligible at 300 bar, yet was ~ 0.2 wt% at 450 bar. At 600 bar the same 20°C increase in temperature almost doubled the solubility with an increase of approximately 0.5 wt%. It is also noted that the isobar at 600 bar was a straight line, showing that at this pressure the solubility of poly (DL-lactide), MW = 2,000, varied linearly with temperature.

The solubility of poly (DL-lactide), molecular weight 9,000 is presented in Figure 4.3 and Figure 4.4.

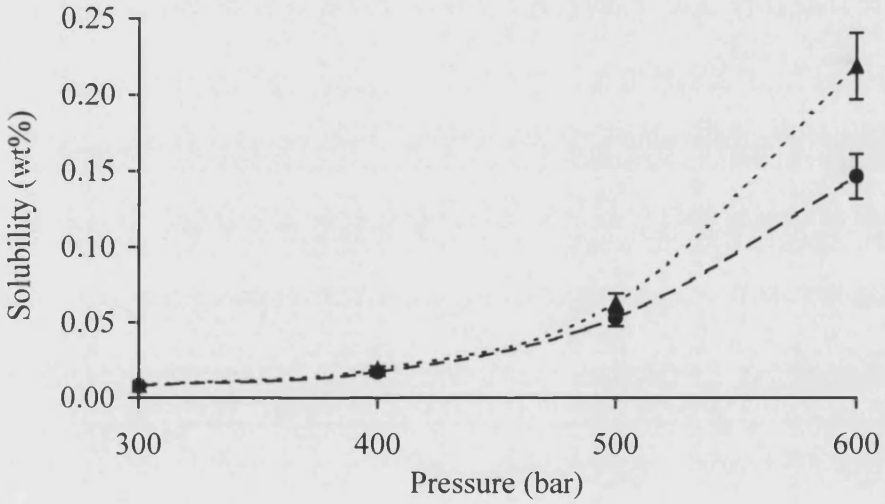



**Figure 4.3.** Solubility isotherms for poly (DL-lactide), MW = 9,000 in carbon dioxide at temperatures:
--▲---45°C, —●—35°C

Figure 4.3 shows the effect of pressure upon the solubility at two temperatures. As before it is seen that increasing the pressure led to an increase in solubility, at both temperatures studied. Again, a fixed increase in the pressure led to a greater increase in solubility at the higher temperature.

From Figure 4.4 it can be seen that changing the temperature from 35°C to 45°C had little effect at 300 and 400 bar. At 500 bar the same 10°C increase in temperature led to a small increase in solubility. At 600 bar, however there was an increase in solubility of approximately 50%, from 0.146 to 0.219 wt%. As this polymer was only studied at two temperatures it is not possible to say whether the solubility varies

linearly with temperature at 600 bar, as with the lower molecular weight poly (DL-lactide).

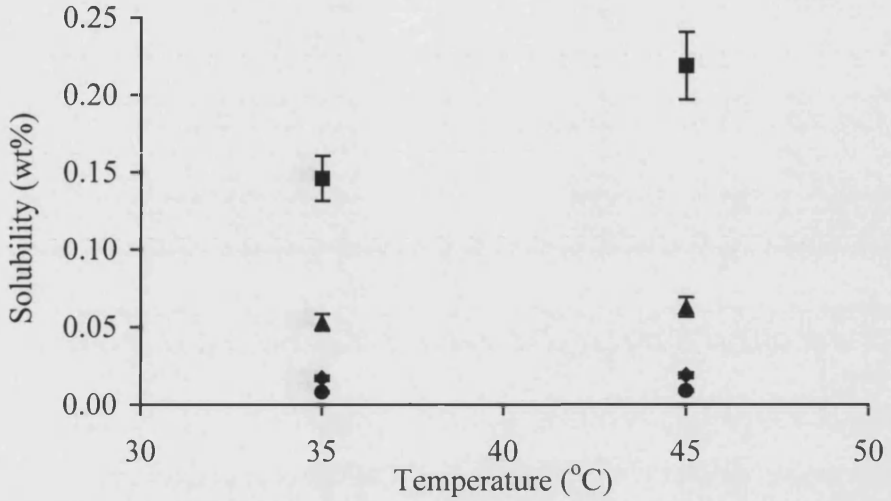



**Figure 4.4.** Solubility isobars for poly (DL-lactide), MW = 9,000 in carbon dioxide at pressures:

■ 600 bar, ▲ 500 bar, ◆ 400 bar, ● 300 bar

### 4.2.1. The Effect of Molecular Weight

A comparison of Figure 4.1 (poly (DL-lactide), MW 2,000) and Figure 4.3 (poly (DL-lactide), MW 9,000) shows the effect which molecular weight has on this solute. It is seen from Figure 4.1 that the lower molecular weight polymer has a solubility of >0.8 wt% at 600 bar and 45°C, whereas from Figure 4.3, the higher molecular weight polymer has a solubility of only 0.23 wt% under the same conditions. Further evidence of this trend is seen in Section 4.1. From Table 4.1 the solubility of poly (DL-lactide), MW 105,000, was 0.014 wt% at 600 bar and 55°C. At the same conditions, this polymer with a molecular weight of 2,000 had a solubility of 1.094 wt%, two orders of magnitude greater than that of molecular weight 105,000. It has therefore been demonstrated that the solubility of poly (DL-lactide) will decrease by approximately an order of magnitude as the molecular weight increases by the same.

## 4.3. Poly (DL-lactide-co-glycolide)

The solubility of poly (DL-lactide-co-glycolide) MW 3,000 is presented in Figure 4.5 and Figure 4.6.

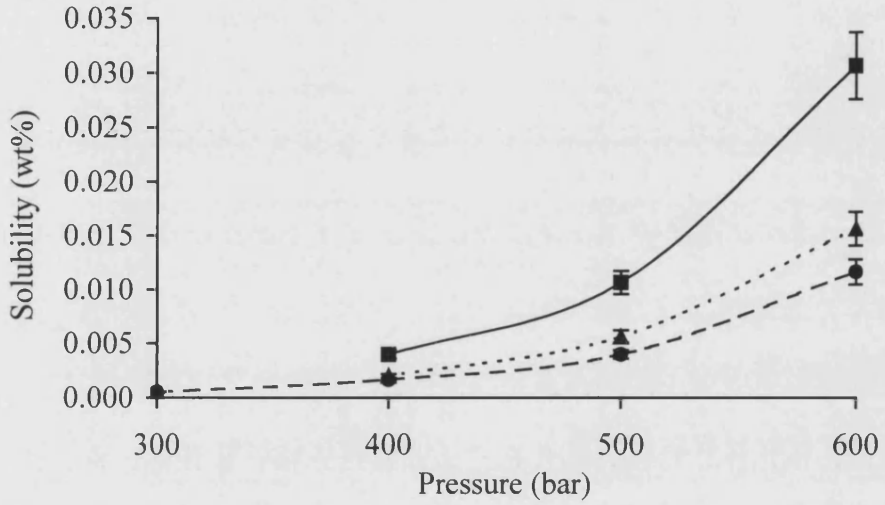



**Figure 4.5.** Solubility isotherms for poly (DL-lactide-co-glycolide) MW = 3,000 in carbon dioxide at temperatures:

—■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C

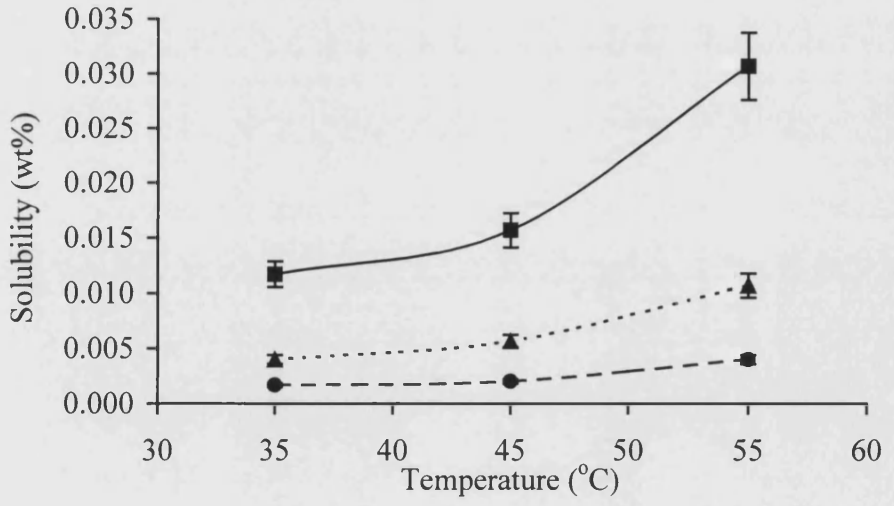



**Figure 4.6.** Solubility isobars for poly (DL-lactide-co-glycolide) MW = 3,000 in carbon dioxide at pressures:

—■— 600 bar, - - ▲ - - 500 bar, — ● — - 400 bar

The solubility of poly (DL-lactide-co-glycolide), Figure 4.5 and Figure 4.6, is between one and two orders of magnitude less than that of poly (DL-lactide), Figure 4.1 and Figure 4.2, although the same general trend is repeated. Increasing the pressure and increasing the temperature each give rise to an increase in the solubility measured. Again, a specific increase in the pressure gave rise to a greater increase in solubility at higher temperatures than at lower ones. An increase in pressure from 400 to 600 bar gave a rise in solubility of 0.27 wt% at 55°C, but only 0.010 wt% at 35°C.

At the lowest pressure of 400 bar, increasing the temperature by 20°C gives a small increase in solubility, from 0.001 to 0.004 wt%. It should be noted that this small increase is only noticeable because the solubility of poly (DL-lactide-co-glycolide) is so low. As the pressure is increased the effect of temperature change on solubility becomes greater. At 600 bar, increasing the temperature from 35°C to 55°C more than doubles the solubility, increasing it from 0.012 to 0.031 wt%.

### 4.3.1. The Effect of Molecular Weight

If the solubility of poly (DL-lactide-co-glycolide) of MW 62,000 at 65°C and 600 bar (Table 4.1) is compared to that of MW 3,000, at 55°C and 600 bar (Figure 4.5) it is seen that they differ by more than an order of magnitude, amounting to 0.002 wt% and 0.031 wt% respectively. This confirms the observation made for poly (DL-lactide) in Section 4.2.1, that increasing the MW of the solute by an order of magnitude has the effect of reducing the solubility by approximately an order of magnitude.

## 4.4. Lactic Acid

In order to gain a clearer picture of the trends seen for the solubility of poly (DL-lactide) in supercritical carbon dioxide, the basic monomer for this material, lactic acid, was studied in detail. Lactic acid is a liquid at room temperature and therefore

the equilibrium cell was modified as detailed in Section 3.4. The solubility isotherms and isobars are shown in Figure 4.7 and Figure 4.8.

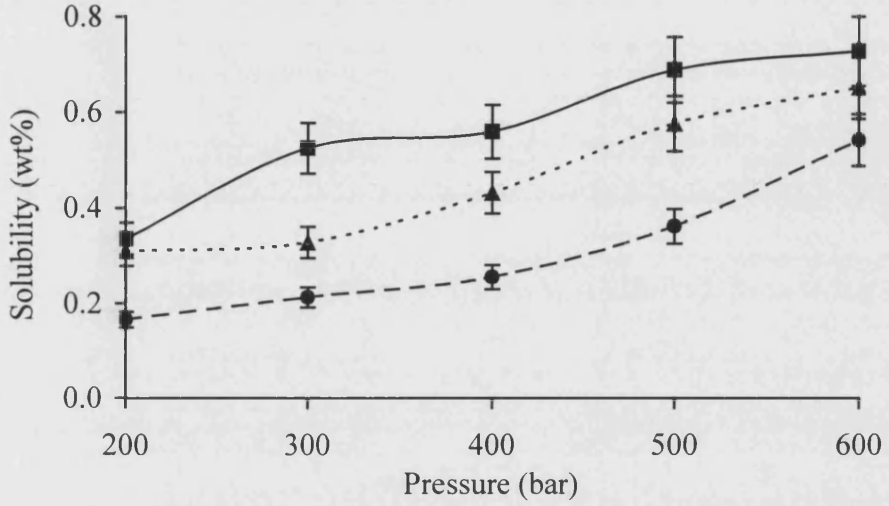



**Figure 4.7.** Solubility isotherms for lactic acid in carbon dioxide at temperatures:

—■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C.

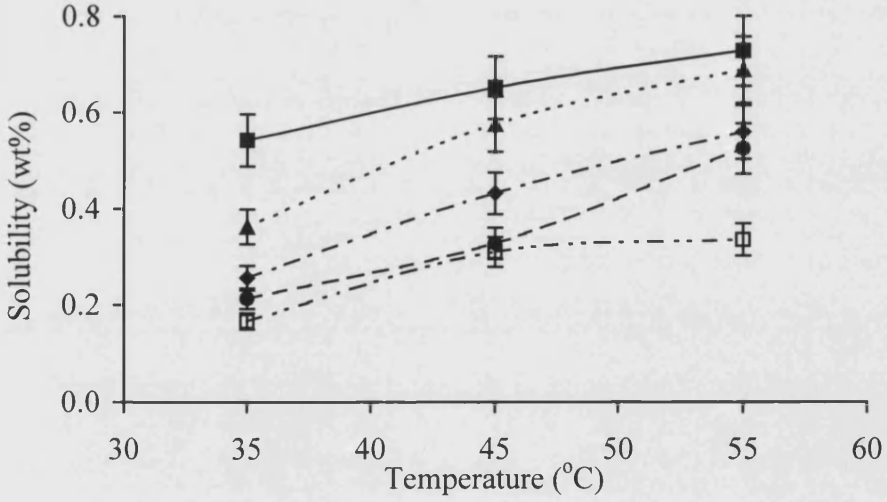



**Figure 4.8.** Solubility isobars lactic acid in carbon dioxide at pressures:

—■— 600 bar, - - ▲ - - - 500 bar, — ◆ - - 400 bar — ● — - 300 bar

— · · ⊞ · · -200 bar

The solubility of lactic acid always increased with increasing pressure or temperature. Unlike poly (DL-lactide) and poly (DL-lactide-co-glycolide) there was little interdependence between temperature and pressure. Changing the temperature always had a large effect on the solubility of lactic acid, regardless of the pressure. Raising the temperature from 35°C to 55°C lead to an increase in solubility of approximately 0.32 wt% at 300, 400 and 500 bar. At 200 and 600 bar, the rise in solubility on increasing the temperature by 20°C was less than this, but still large. An increase in pressure from 200 to 600 bar gives a rise in solubility of approximately 0.35 wt% at all three temperatures studied. It would appear that the effect of pressure on solubility is independent of temperature, and *vice versa,* for the ranges studied.

The points on Figure 4.7 and Figure 4.8 seem rather more scattered than those for the polymers looked at earlier; probably an indication that the results for lactic acid are not as reliable as those for the polymers. This is possibly due to lactic acid being in the liquid phase. High solubilities may have been measured due to entrained droplets of liquid being carried over into the cold trap by the flow of carbon dioxide. Low solubilities may have been measured because there was less contact between the solute and the solvent than would occur with a solid, hence equilibrium may not have been reached in some cases. In spite of this, conclusions on the general solubility trends can be drawn with confidence.

## 4.5. Eudragit® RL100

The results presented in Figure 4.9 are averages of at least 3 measurements, all taken when there was no visible evidence of swollen polymer being carried over, as considerable problems were experienced when attempting to measure the solubility of this material. From the work of Ehrlich (1992), it was thought that the polymer was swollen in the presence of supercritical carbon dioxide. This was assumed to reduce the glass transition temperature of the polymer, as it was clearly mobile. The swollen material passed through the glass wool plug and the stainless steel frit at the top of the equilibrium cell, and large quantities were carried over, into the cold trap.

This phenomenon was observed regularly after the cell had been filled, but was also seen to take place irregularly at other times, and led to erroneous results on a number of occasions.

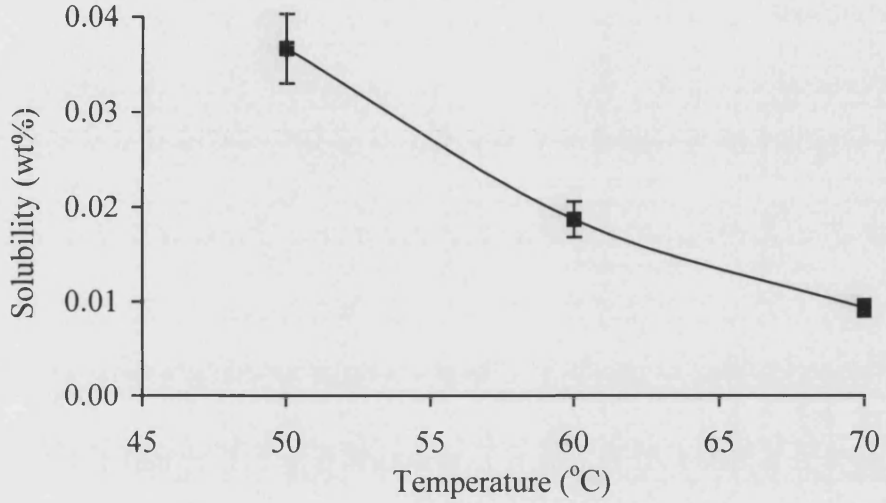



**Figure 4.9.** Solubility isobar for Eudragit® RL100 in carbon dioxide at 600 bar.

Figure 4.9 shows the effect of temperature on the solubility of Eudragit® RL100. As can be seen, the solubility decreases as the temperature is increased. This is different to the trend seen for poly (DL-lactide) and poly (DL-lactide-co-glycolide) where increasing the temperature would either increase solubility, or have no effect on it.

The effect of pressure on the solubility of Eudragit® RL100 was not considered due to the problems of obtaining accurate results when using a swollen polymer. All the work done on the solubility of polymers in supercritical fluids to date has shown that solubility increases with increasing pressure. This trend is expected to be true for Eudragit® RL100.

## 4.6. The Morphology of Materials Collected in Cold Trap

It was noted during the above experiments, which measured the solubility of polymers in supercritical carbon dioxide, that the condition of the material collected in the cold trap varied. During the process of dissolving, and precipitating out of solution, the materials changed their physical form. Observations regarding the nature of the materials collected were made to assist in characterising these systems more fully. On one occasion it was possible to take particle size measurements.

### 4.6.1. Poly (DL-lactide)

Poly (DL-lactide) always formed a powder in the cold trap at all the conditions and molecular weights studied. At the higher solubility conditions, the powder was collected principally in the bottom of the U-tube, although some adhered to the sides of the tube, mainly on the inlet side. Some powder had also passed the full length of the U-tube, and before being caught in the plug of glass wool in the outlet. At lower solubilities, most of the powder collected had adhered to the sides of the U-tube, below the inlet.

As poly (DL-lactide) MW 2,000 was the most soluble polymer, sufficient was collected in the U-tube to conduct particle size measurements. These are described in Section 3.5; the results are presented in Table 4.2 and Figure 4.10 and Figure 4.11.

**Table 4.2.** Particle sizes for poly (DL-lactide) MW 2,000

| Material | Mean particle size (μm) | Standard deviation (μm) |
|---|---|---|
| Poly (DL-lactide), MW 2,000, as received | >500 | 191 |
| Poly (DL-lactide), MW 2,000, dissolved in $SCCO_2$ at 600 bar and 45°C | 75 | 69 |

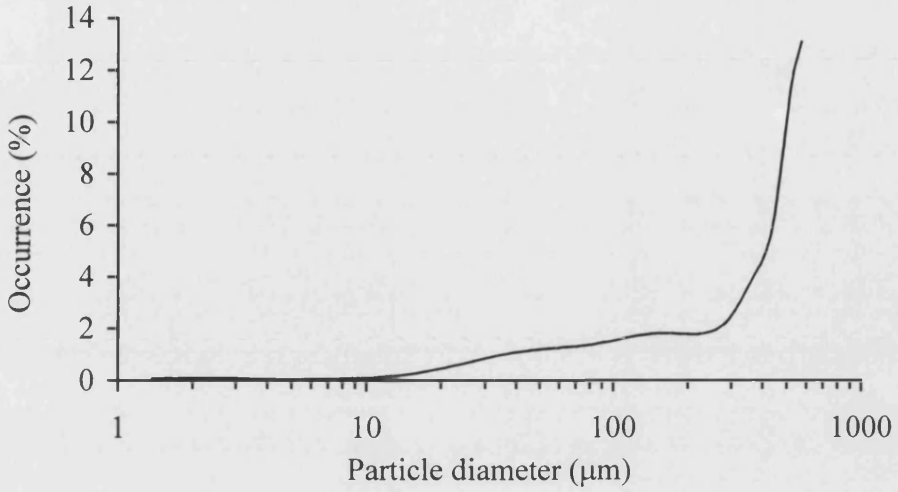



**Figure 4.10.** Distribution curve for particles of poly (DL-lactide) MW 2,000, as supplied

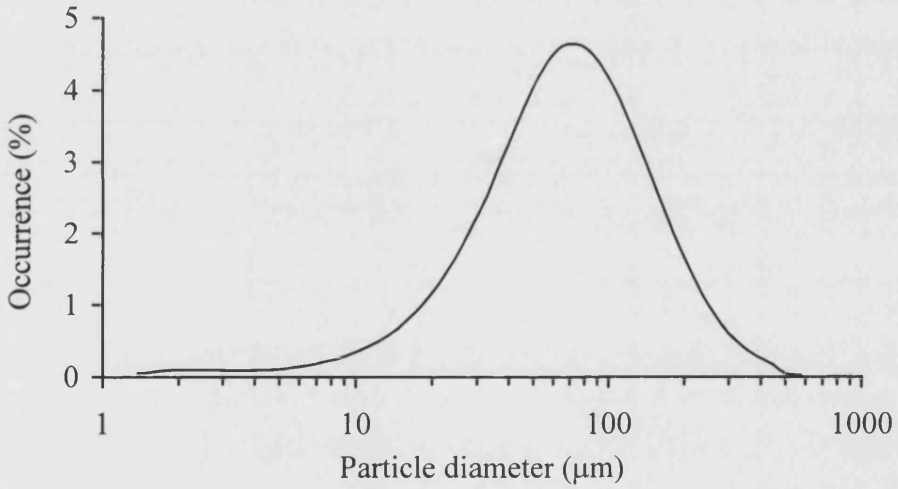



**Figure 4.11.** Distribution curve for particles of poly (DL-lactide) MW 2,000 collected following solubilisation in carbon dioxide at 600 bar and 45°C

From Figure 4.10 the material supplied by the manufacturer consists of particles with a wide range of sizes. There is some fine powder, but the majority of the material was in larger particles. The Mastersizer is only capable of measuring particle sizes up to 600μm and therefore it is not possible to characterise this material fully.

From Table 4.2 the mean diameter of the particles produced when poly (DL-lactide) is dissolved in supercritical carbon dioxide at 600 bar and 45°C, and then precipitated rapidly out of solution is 75 μm. There was a large size reduction during this process, and the curve shown in Figure 4.11 describes a normal distribution.

Poly (DL-lactide) MW 9,000 was not sufficiently soluble in supercritical carbon dioxide to be able to collect a sample to measure particle sizes.

### 4.6.2. Poly (DL-lactide-co-glycolide)

The material collected in the cold trap was deposited in much the same way as the poly (DL-lactide), Section 4.6.1. The material caught in the cold trap was a fine white powder which adhered to the wall of the cold trap, below the inlet point. Some was also deposited in the bottom of the trap, and was seen in the glass wool plug. The solubility of poly (DL-lactide-co-glycolide) was lower than that of poly (DL-lactide), MW 9,000, and insufficient was collected in the U-tube to enable particle size measurements.

### 4.6.3. Eudragit® RL100

The Eudragit® RL100 which collected in the cold trap appeared as larger particles, of approximate size 1-2 mm. These collected at the bottom of the U-tube, unlike the fine powder seen for poly (DL-lactide) and poly (DL-lactide-co-glycolide) which tended to adhere to the sides of the tube. The particles were irregularly shaped and were white in colour, and opaque, compared with the semi translucent white of the starting material. No accurate particle size measurements were taken as the Eudragit® RL100 particles were too large for the Mastersizer, which measured to a maximum size of 600 μm. No particles or powder adhered to the walls of the tube, and the material was not carried through the U-tube to be trapped in the glass wool plug.

On a number of occasions, large quantities of swollen Eudragit® RL100 were carried over into the cold trap. A sample is shown in Figure 4.12.

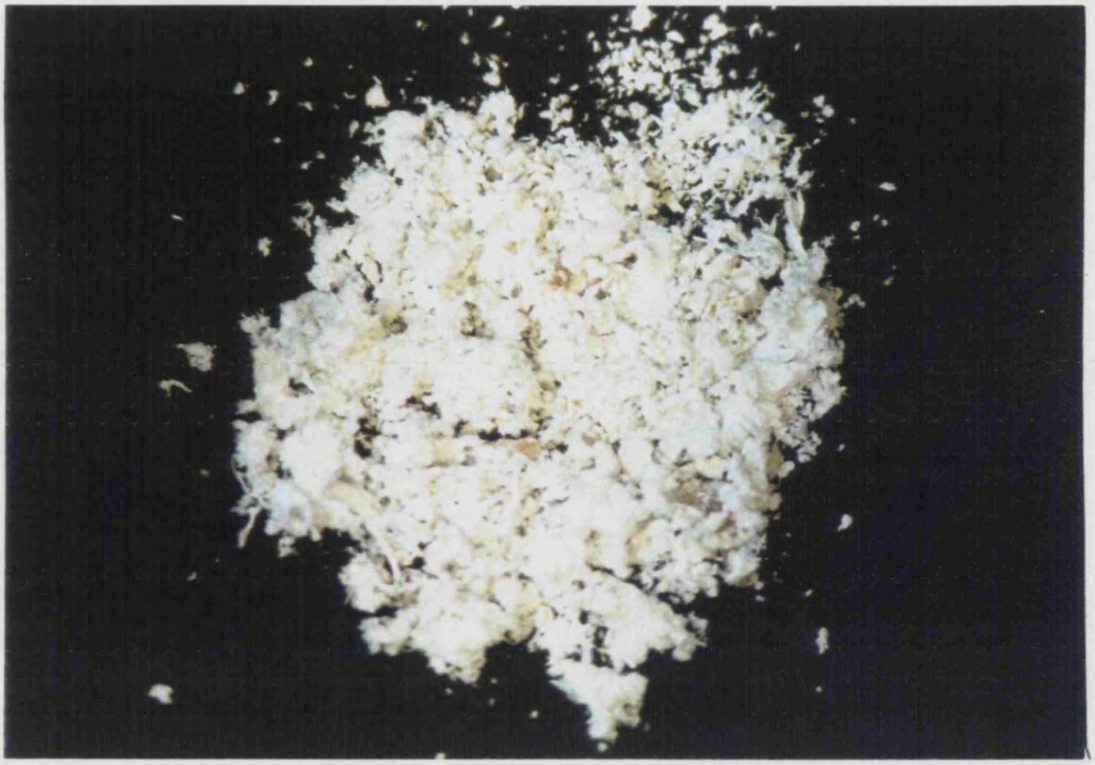



**Figure 4.12.** Swollen Eudragit® RL100 collected in the cold trap.

This material was white and porous, and felt softer and less dense than the hard particles of Eudragit® RL100 collected normally. When this phenomenon occurred, the swollen material was deposited quickly in the U-tube, rather than the slow deposition which was characteristic of most solubility experiments.

## 4.7. The Nature of the Polymer Residues in the Cell

Following the solubility measurements, the material remaining in the cell was examined visually to see if it had undergone any physical change due to exposure to supercritical carbon dioxide.

### 4.7.1. Eudragit® RL100

This material was supplied as a granular solid; each granule was approximately cubic in shape, and had a Feret's diameter of approximately 3 mm. The granules were white/semi-translucent in colour, and when examined under magnification (x5) were seen to be solid with no obvious pores present.

Following the solubility measurements the polymer in the equilibrium cell had undergone a physical change into a solid cylinder, which was opaque and white in colour. The cylinder of Eudragit® RL100 was a tight fit in the equilibrium cell and it had clearly swollen in the presence of supercritical carbon dioxide. Further evidence of this was that the glass wool plug, at the top of the equilibrium cell, and the ballotini packed at the bottom was incorporated in the polymer cylinder.

Upon removal from the cell, the swollen cylinder was snapped into two. The cylinder form was homogeneous, with no sign of the original granular structure. On examination with a magnifying glass the structure was obviously very porous. This was borne out by its low density of 0.46 g/cm$^3$, compared with a density of 1.1 g/cm$^3$ for the parent material.

In order to establish the conditions of temperature and pressure required for this swelling phenomena to take place, and also to establish the rate at which it occurred, further experiments were carried out as described in Section 3.5.2, at the conditions shown in Table 4.3.

The materials formed in experiments 1 and 2 were as described previously in this section; the polymer was white in colour, porous, light in weight and homogeneous. It was hard and brittle; a bending moment caused the cylinder to snap rather than bend. A piece of the material formed in experiment 1 is shown in Figure 4.13. It has a diameter of 18 mm, the internal diameter of the equilibrium cell, and is approximately 75 mm long. The ends are those obtained as the material was snapped into pieces. The pores present in the material run along the length of the cylinder, thus enabling the flow of carbon dioxide.

**Table 4.3.** Eudragit® RL100 Swelling Experiments

| Experiment Number | Temperature °C | Pressure Bar | Time Minutes |
|---|---|---|---|
| 1 | 50 | 600 | 90 |
| 2 | 60 | 600 | 60 |
| 3 | 50 | 600 | 3 |
| 4 | 40 | 100 | 90 |
| 5 | 40 | 75 | 90 |

Experiment 3 was carried out at the same conditions as experiment 1, with the exception of the length of time left at pressure. Pressure (600 bar) was maintained for 3 minutes, with a minute to pressurize the rig, and approximately 5 minutes to depressurize. The material produced, (Figure 4.14), was in physical appearance intermediate between the starting material and that obtained during experiment 1. The individual granules were still visible; they had all expanded, and adhered to each other, but were still identifiable as the granules initially loaded into the cell. The cylinder was not as strong as that produced in experiment 1 and snapped easily along the granular boundaries. The right hand end of the material shown in Figure 4.14 was produced when the cylinder was broken in two. When viewed end on the cylinder of polymer produced was not uniform. The granules in the centre of the cell had not expanded, and still looked semi-transparent, compared with the white porous granules which had been situated near the cell wall. From this it was concluded that even with the high diffusivity of supercritical carbon dioxide, it takes a significant length of time for the carbon dioxide to diffuse into the polymer and cause it to swell.

At the lower pressures of experiments 4 and 5, the materials produced took the form of white, porous cylinders of polymer which were uniform throughout. They were the same as those produced initially, and in experiments 1 and 2.

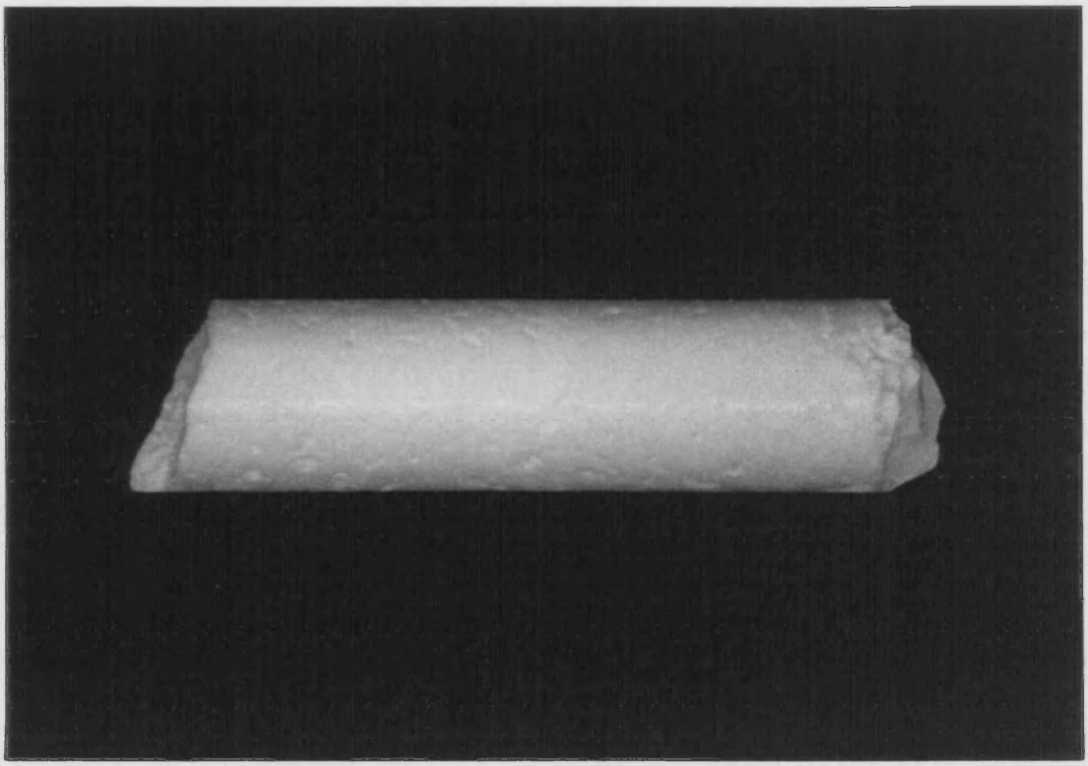



**Figure 4.13.** Eudragit® RL100 formed in experiment 1

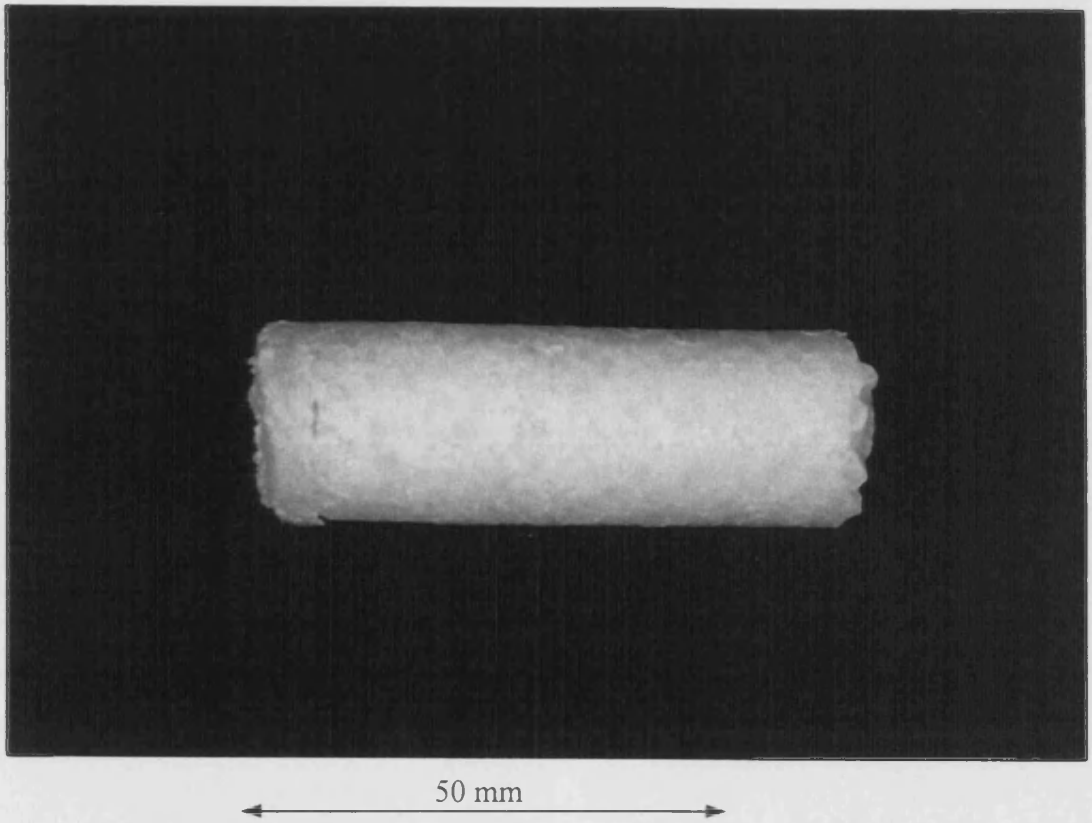



**Figure 4.14.** Eudragit® RL100 formed in experiment 3

### 4.7.2. Poly (DL-lactide) and Poly (DL-lactide-co-glycolide)

While it was noted above that Eudragit® RL100 swelled in the presence of supercritical carbon dioxide, and changed its physical form, there was no evidence that the same phenomenon occurred with poly (DL-lactide) or poly (DL-lactide-co-glycolide). When these materials were removed from the cell, after performing solubility measurements at the range of temperatures and pressures shown in Figure 4.1 to Figure 4.6, they did not appear to have undergone any physical change.

**Table 4.4.** Summary of solubility results

| Material | Molecular Weight | Temperature (°C) | Pressure (bar) | Solubility (wt%) |
|---|---|---|---|---|
| Poly (DL-lactide) | 2,000 | 35 | 300 | 0.189 |
| | | | 450 | 0.320 |
| | | | 600 | 0.623 |
| | | 45 | 300 | 0.189 |
| | | | 450 | 0.327 |
| | | | 600 | 0.859 |
| | | 55 | 300 | 0.195 |
| | | | 450 | 0.539 |
| | | | 600 | 1.094 |
| Poly (DL-lactide) | 9,000 | 35 | 300 | 0.008 |
| | | | 400 | 0.017 |
| | | | 500 | 0.053 |
| | | | 600 | 0.146 |
| | | 45 | 300 | 0.009 |
| | | | 400 | 0.019 |
| | | | 500 | 0.063 |
| | | | 600 | 0.219 |

**Table 4.4.** Summary of solubility results (continued)

| Material | Molecular Weight | Temperature (°C) | Pressure (bar) | Solubility (wt%) |
|---|---|---|---|---|
| Poly (DL-lactide-co-glycolide) | 3,000 | 35 | 300 | 0.001 |
| | | | 400 | 0.002 |
| | | | 500 | 0.004 |
| | | | 600 | 0.012 |
| | | 45 | 400 | 0.002 |
| | | | 500 | 0.006 |
| | | | 600 | 0.016 |
| | | 55 | 400 | 0.004 |
| | | | 500 | 0.011 |
| | | | 600 | 0.031 |
| Eudragit® RL100 | >100,000 | 50 | 600 | 0.037 |
| | | 60 | 600 | 0.019 |
| | | 70 | 600 | 0.009 |
| Lactic acid | 90 | 35 | 200 | 0.166 |
| | | | 300 | 0.213 |
| | | | 400 | 0.256 |
| | | | 500 | 0.362 |
| | | | 600 | 0.542 |
| | | 45 | 200 | 0.310 |
| | | | 300 | 0.328 |
| | | | 400 | 0.432 |
| | | | 500 | 0.576 |
| | | | 600 | 0.652 |
| | | 55 | 200 | 0.336 |
| | | | 300 | 0.525 |
| | | | 400 | 0.560 |
| | | | 500 | 0.689 |
| | | | 600 | 0.728 |

# Chapter 5. Discussion

In this chapter, each material is discussed with reference to the solubility trends seen in Chapter 4. The ubiquitous coating material hydroxypropylmethylcellulose, (HPMC), is discussed first, although its solubility is low and hence limited data was collected.

The solubility of the polymer poly (DL-lactide), an excipient with the potential to be used as a controlled release coating, is discussed, and an evaluation made of the effect of changing its molecular weight. The effect of small changes in the chemistry of the monomers used to form the polymers was then examined by measuring the solubility of poly (DL-lactide-co-glycolide). In this material a methyl group is replaced by a hydrogen group in half of the monomer units, when compared to poly (DL-lactide).

Hypotheses are offered to explain the solubility trends discussed for poly (DL-lactide) and poly (DL-lactide-co-glycolide). These are supported by further evidence gained from the solubility of lactic acid, the starting material when making poly (DL-lactide).

Eudragit® RL100 is, by contrast a high molecular weight compound of rather different characteristics to the poly (DL-lactide) and poly (DL-lactide-co-glycolide). It is used as an enteric coating and is insoluble in water. The physical changes undergone by Eudragit® RL100 in the presence of supercritical carbon dioxide are discussed fully in Section 5.7, as these may have an effect on the usefulness of carbon dioxide as a solvent for processing pharmaceutical excipients.

The effects of temperature and pressure on solubility are better demonstrated using solubility verses density plots, and this has been done in Section 5.6. The gradients and intercepts of these straight line plots are calculated. These constants can be used to extrapolate solubility data with a reasonable degree of confidence.

## 5.1. Hydroxypropylmethylcellulose, (HPMC)

It was found from the initial screening work that the solubility of HPMC was very low; only 0.008 wt% at 600 bar and 60°C (Table 4.1). For a typical film coated tablet which may weigh 0.5g, the coating amounts to approximately 2.5% of the weight of the tablet, therefore a typical tablet would require 12.5mg of coating material. As current coating methods are inefficient, up to half of the coating material would either adhere to the coater, or be carried out of the process by the air flow and be wasted. In this case approximately 20mg of coating material would be required per tablet. By calculation 250g of carbon dioxide at 600 bar and 60°C would be required to solubilize the 20mg of HPMC coating material for one tablet. A typical batch of tablets may number 10,000, requiring 200g of HPMC and 2.5 tonnes of carbon dioxide. This is a vast amount of solvent and would obviously be prohibitively expensive in terms of solvent use, energy costs for compression, and time taken to perform the coating.

As noted previously, HPMC is water soluble, and is currently used as an inexpensive film coating material in relatively large quantities by the pharmaceutical industry. In the example above, the batch of 10,000 tablets would require only a few litres of aqueous solution, rather than 2.5 tonnes of carbon dioxide solution. A coating system based on supercritical fluid technology for HPMC would therefore be inefficient, impractical and not economically viable.

## 5.2. Poly (DL-lactide)

As noted in Section 4.2, increasing the pressure and the temperature in the cell gave rise to an increase in the solubility of poly (DL-lactide) in supercritical carbon dioxide. As the pressure increased so did the density and dielectric constant of the carbon dioxide (Michels and Michels, 1933). This led to an increase in the solvent power of the carbon dioxide, and hence the measured solubility. Temperature however tended to exert the opposite effect on the solute; an increase in temperature decreased the density and dielectric constant of the carbon dioxide and tended to

depress the solubility. The increase in the solubility which was measured can be explained by considering the effect of the temperature on the solute. An increase in temperature tended to increase the vapour pressure of the solute (Prausnitz *et al.*, 1986, 416-417) thus making the solute easier to dissolve. At lower pressures a change in temperature had a similar effect on both the solute and the solvent as there was little increase in solubility with rising temperature. At higher pressure however, the change in the properties of the solute was the dominant factor as there was a large change in solubility when temperature was varied.

### 5.2.1. Effect of Molecular Weight on Solubility

It was noted in Section 4.2.1 that increasing the molecular weight of the poly (DL-lactide) caused a decrease in the solubility in supercritical carbon dioxide. This confirmed the trend noted in the literature, and is logical that the larger molecules should be more difficult to solubilize than smaller ones. It is known that as the molecular weight of a solid, and hence the size of the molecules are increased the attractive forces between the molecules becomes greater. The vapour pressure of the solid and hence its solubility would therefore decrease.

## 5.3. Poly (DL-lactide-co-glycolide)

As was seen in Section 4.3 the solubility of poly (DL-lactide-co-glycolide) followed the same trend as for poly (DL-lactide), and therefore the same reasons are assumed to hold true. Increasing pressure increased the density and dielectric constant of the carbon dioxide, hence leading to an increase in the solubility. Raising the temperature led to an increase in the vapour pressure of the solute, together with a decrease in the density and dielectric constant of the carbon dioxide. At low pressures these effects almost cancel each other out, yet at high pressures the effect of temperature on the solute was greater.

The other important observation from Section 4.3 is that the solubility of poly (DL-lactide-co-glycolide) MW 3,000 is an order of magnitude less than that of poly (DL-

lactide) MW 9,000. It is therefore concluded that the chemical structure of the polymers has a large effect on the solubility measured. It is noted from Figure 4.3 and Figure 4.5, that the solubility of poly (DL-lactide-co-glycolide) is an order of magnitude less than that of poly (DL-lactide), even though the molecular weight of poly (DL-lactide) is considerably higher. The manufacturers literature states that both poly (DL-lactide) and poly (DL-lactide-co-glycolide) are soluble in most conventional solvents such as acetone, however it does not state how soluble they are. Poly glycolide is not soluble in conventional solvents. It appears that the presence of the glycolide molecules in the co-polymer is responsible for the reduction in solubility seen.

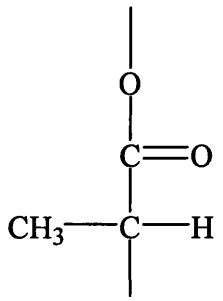


**Figure 5.1.** Lactide monomer

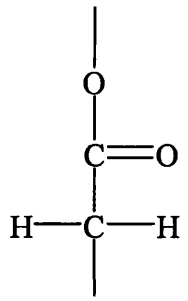


**Figure 5.2.** Glycolide monomer

The structures of the lactide and glycolide monomers are shown in Figure 5.1 and Figure 5.2. The only difference is the presence of the $CH_3$ group on the lactide monomer, which is not present on the glycolide. It is known that oxygen is more electronegative than carbon and therefore there will be some polarization in both the lactide and glycolide monomers. The carbonyl group particularly will tend to be negatively charged and hence this will cause the polarization. The effect of this on the glycolide monomer is to impart a positive charge to the hydrogen atoms present; hence hydrogen bonding between glycolide monomers can take place. The presence of the methyl group on the second carbon in the lactide monomer results in the positive charge being diffused rather than concentrated on the two hydrogen atoms as with glycolide. This means hydrogen bonds are less likely to occur as the concentration of the positive charge is less.

The poly (DL-lactide-co-glycolide) used for this work was composed of 50 % lactide and 50 % glycolide monomer. It is hypothesized that the large increase in the hydrogen bonding due to the presence of the glycolide in the co-polymer is responsible for the large reduction in solubility of this material when compared with poly (DL-lactide). As stated previously, carbon dioxide is a non-polar covalent molecule, and hence is not expected to dissolve polar, hydrogen bonded materials.

## 5.4. Lactic Acid

It was noted in section 4.4 that the solubility of lactic acid in supercritical carbon dioxide was approximately the same order of magnitude as poly (DL-lactide), MW 2,000. This is somewhat surprising as the molecular weight of lactic acid is only 90. To explain this apparent anomaly one needs to consider the chemical properties of this material in a similar manner to that above.

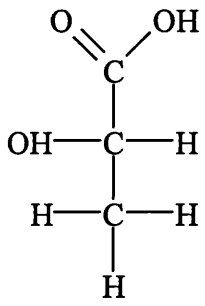



**Figure 5.3.** Lactic acid molecule

Lactic acid is a polar molecule, as shown in Figure 5.3, and will form strong hydrogen bonds. As noted in Section 5.3, poly (DL-lactide) will not tend to form hydrogen bonds as the positive charge is diffused over a larger area. Therefore, although the low molecular weight of lactic acid when compared to poly (DL-lactide) would tend to suggest that lactic acid is more soluble in supercritical carbon dioxide, the difference in chemical properties negates this effect. In fact lactic acid is between 13 and 33 % less soluble than poly (DL-lactide), MW 2,000 at high pressure (600 bar), and the temperatures studied.

It is interesting to note that with this small molecule, temperature has a large effect on solubility even at the lower pressures. It would seem that as the molecular weight of the solute increases, the pressure required for an increase in temperature to give rise to an increase in solubility becomes higher. It is seen from Figure 4.4 that temperature has no effect on the solubility of higher molecular weight poly (DL-lactide) until the pressure is approximately 600 bar. From Figure 4.2, temperature has a significant effect on solubility at 450 bar for low molecular weight poly (DL-lactide), and from Figure 4.8 temperature has a significant effect on lactic acid at all pressures studied from 200 bar upwards.

As noted earlier increasing the temperature of a supercritical system has two effects;

a) it reduces the density and dielectric constant of the carbon dioxide, hence reducing the solubility of solute therein,

b) it increases the vapour pressure of the solute, increasing the solubility of that solute.

At lower pressures an increase in temperature has a larger effect on reducing the density of supercritical carbon dioxide than at higher pressures.

From Figure 5.4, the density of supercritical carbon dioxide is reduced by almost 100 $kg/m^3$ when the temperature is increased from 35°C to 55°C at 300 bar. At 600 bar however, the density reduction is only 60 $kg/m^3$ for the same temperature increase. This would appear to explain the solubility trends seen. It is assumed that a set increase in temperature gives the same increase in vapour pressure of the solute, regardless of the pressure.

From Section 5.2 it was seen that increasing the temperature leads to an increase in the solubility of these relatively low molecular weight polymers. From this, the conclusion that changing the temperature has a more significant effect on the vapour pressure of the solute than on the density of the carbon dioxide has been drawn. It

can now be concluded that the increase in vapour pressure of a small molecule, on increasing the temperature, is greater than that for a similar but larger molecule.

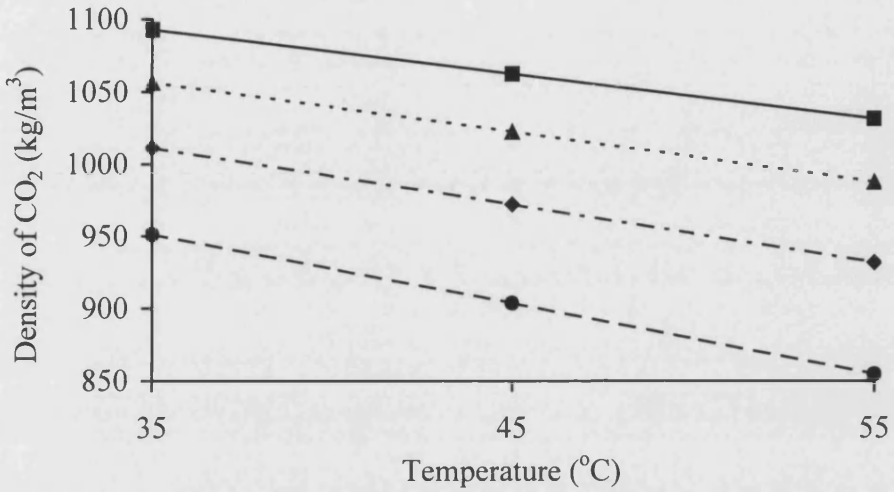



**Figure 5.4.** The variation of density of carbon dioxide with temperature at pressures:

—■— 600 bar, - - ▲ - - - 500 bar, — ◆ - - 400 bar, — ● — - 300 bar

(data from Vukalovich and Altunin, 1965)

For lactic acid, the material with the smallest molecular weight, increasing temperature always has a greater effect on the vapour pressure of the solute than on the density and dielectric constant of the solvent, hence solubility was always seen to increase. For poly (DL-lactide), MW 9,000, the effect of temperature change on both the solute and the solvent approximately cancels each other out at pressures of 300-500 bar. It is only at 600 bar, when the reduction in density of supercritical carbon dioxide is lowest on increasing the temperature, that the solubility increases significantly. Poly (DL-lactide) of MW 2,000 would therefore be expected to fall between these two materials. Figure 4.2 confirms this; a significant increase in solubility seen on increasing the temperature at 450 bar, but not at 300 bar.

In the above discussion pressure has not been considered in detail. Atkins (1990) notes that as the pressure of a liquid is increased, its vapour pressure increases also. This in itself would tend to increase solubility. It is generally assumed that the

vapour pressure of a solid is independent of the system pressure. This would appear to be a reasonable assumption as in the cases studied an increase in pressure always resulted in an increase in the solubility measured.

## 5.5. Eudragit® RL100

As noted in Section 4.5 the solubility of Eudragit® RL100 was highest at the lowest experimental temperature, 50°C. As the temperature increased the solubility decreased. The effects of temperature on both the solute and solvent have been noted in Section 5.4. It is hypothesised that the change in temperature has the greatest effect on the properties of the solvent rather than the solute. In Section 5.4 it was concluded that as the molecular weight of the solute increased, so did the pressure required for a rise in temperature to give an increase in the solubility. The largest polymer considered in that section had a molecular weight of 9,000. Eudragit® RL100 has a molecular weight in excess of 100,000. It would therefore seem that for high molecular weight polymers the effect of temperature on the vapour pressure of the solute is very small, and hence the trend seen in Figure 4.9, where solubility decreases with increasing temperature.

## 5.6. Density Correlations

While Figure 4.1 and Figure 4.3 clearly illustrate the general effect of pressure on the solubility of poly (DL-lactide) it is obvious that there is not a simple relationship between pressure and solubility. Likewise from Figure 4.2 and Figure 4.4 the effect of temperature on solubility can be seen but cannot be easily quantified. As described in Section 2.5, Robin & Vodar (1953) noted that log solubility usually varied linearly with density. The solubility data has been replotted in the following figures to assess whether this relationship holds true for poly (DL-lactide), MW 2,000 and 9,000, poly (DL-lactide-co-glycolide), MW 3,000, and lactic acid.

Figure 5.5 shows the variation of log solubility with density for poly (DL-lactide), MW 2,000, at the temperatures studied.

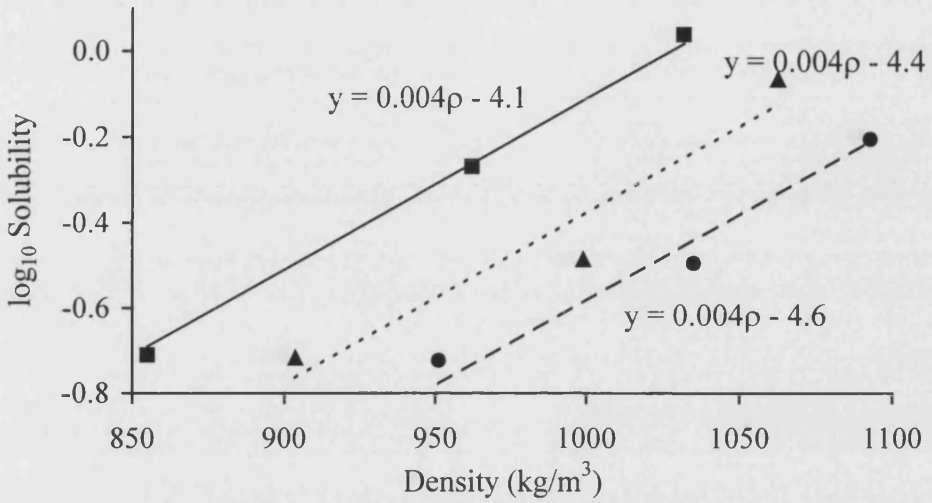



**Figure 5.5.** The variation of solubility of poly (DL-lactide), MW = 2,000 with density of carbon dioxide at temperatures:
—■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C.

From Figure 5.5 the isotherms drawn show a clear linear relationship between log solubility and density at 55°C and 35°C. The relationship is not as clear at 45°C, however this may be due to experimental errors in determining the solubilities at 45°C. It was noted that the gradients of the isotherms did not vary with temperature, thus demonstrating that a fixed increase in density at constant temperature will always give the same increase in log solubility, regardless of the actual temperature. This can also be seen by considering the equations of the isotherms. These are of the form:

$$\log_{10} m = A\rho + B \qquad (5.1)$$

$m$ = solubility, (wt%)

$\rho$ = density of gas (g/cm$^3$)

$A$ = function of material only

$B$ = function of material and temperature

For poly (DL-lactide), the value of *A*, the gradient of the lines, is 0.004, and the value of *B*, the intercept, is -4.1 at 55°C, -4.4 at 45°C and -4.6 at 35°C.

Figure 5.6 shows the relationship between solubility and density for poly (DL-lactide) of MW 9,000 at the temperatures of 35 and 45°C.

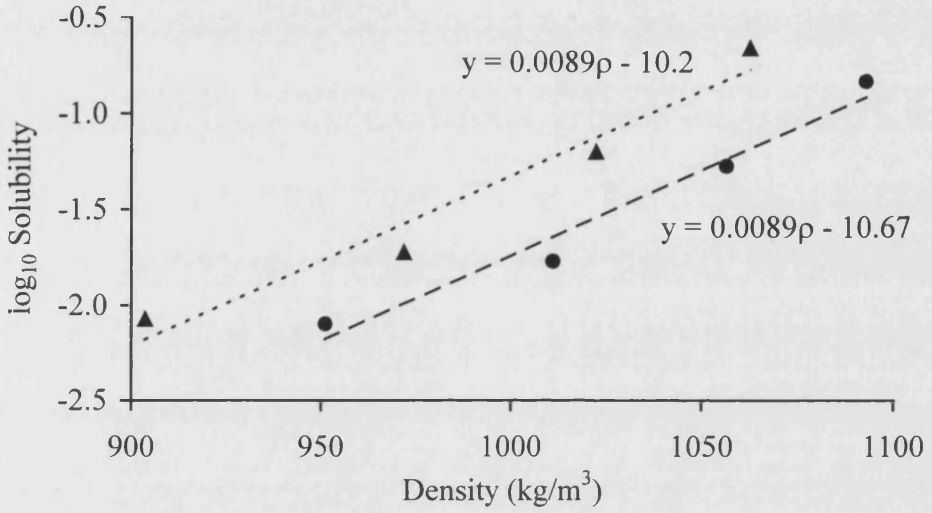



**Figure 5.6.** The variation in solubility of poly (DL-lactide), MW = 9,000 with density of carbon dioxide at temperatures:
- - ▲ - - - 45°C, — ● — - 35°C.

Figure 5.6 shows the same trend as Figure 5.5 with a linear relationship seen between log solubility and density. The lines are again parallel showing that the change in ($\log_{10}$) solubility with changing density is independent of temperature. If Figure 5.5 and Figure 5.6 are compared, the effect of molecular weight on solubility can be considered in more detail.

The intercepts of the lines plotted on Figure 5.6 are considerably lower (more negative) than the intercepts of the lines on Figure 5.5, -10.2 to -10.67, compared with -4.1 to -4.6. This reflects the lower solubilites measured for the polymer with the higher molecular weight. The slope of the lines on Figure 5.6 is considerably steeper (over twice as steep) than the gradient of the lines on Figure 5.5. This indicates a greater change in the log solubility with density for the higher molecular

weight polymer. If the pressure and hence density is increased it appears that there will come a point when the higher molecular weight poly (DL-lactide) is more soluble than the lower molecular weight one. This is dependent upon two conditions: the linear relationships illustrated on Figure 5.5 and Figure 5.6 holding for the carbon dioxide/poly (DL-lactide) systems over the full supercritical range of carbon dioxide; and the density of carbon dioxide continuing to increase indefinitely on increasing the pressure.

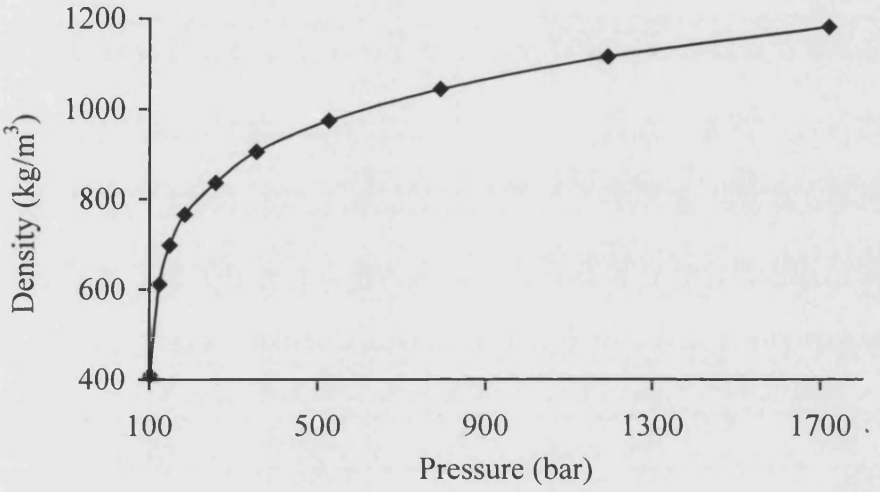



**Figure 5.7.** Variation of density with pressure for carbon dioxide at 49.7°C, data from Michels *et al.* (1935).

From Figure 5.7 it is seen that the second condition does not hold true, and hence the higher molecular weight poly (DL-lactide) will not become more soluble than the lower molecular weight one. While the density of carbon dioxide increases rapidly as the pressure is increased up to approximately 200 bar, above this pressure the rate of increase becomes less, and the density tends towards a maximum value. This trend is expected if one considers the carbon dioxide on a molecular scale. An increase in pressure has the effect of forcing the molecules closer together, thus increasing the density. At low pressures, the supercritical carbon dioxide behaves as a traditional gas and the molecules are widely spaced. These can be easily forced closer, hence the density rises considerably. At higher pressures and densities, the molecules are already in close proximity to one another, and the repulsive forces between them become greater. A rise in pressure now gives a much smaller increase

in density. The maximum will (theoretically) be reached when the carbon dioxide molecules are packed together such that they cannot be compressed any further.

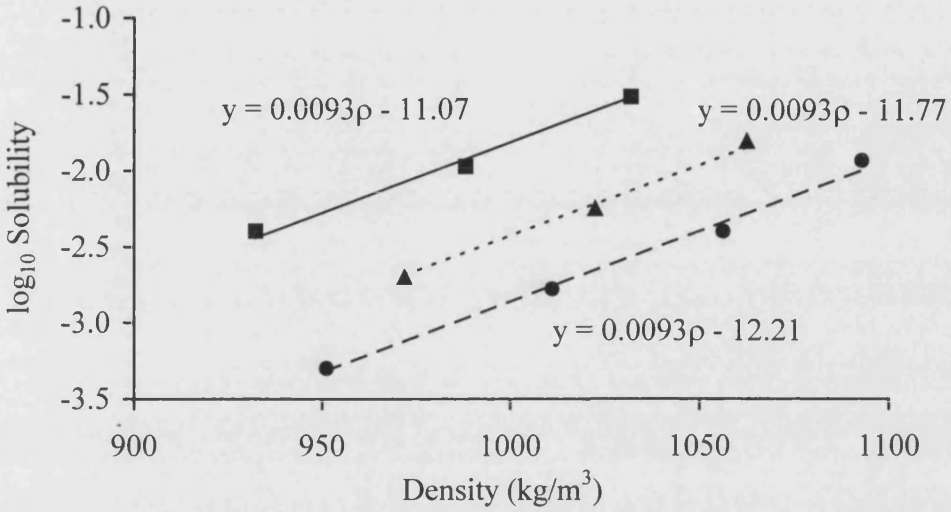



**Figure 5.8.** The variation in solubility of poly (DL-lactide-co-glycolide), MW = 3,000 with density of carbon dioxide at temperatures:
—■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C.

Figure 5.8 shows the plot of $\log_{10}$ solubility against density for poly (DL-lactide-co-glycolide), MW 3,000. This shows the same trends as discussed earlier for poly (DL-lactide); the isotherms produce straight lines, with a slope independent of temperature. The intercepts of these isotherms are slightly lower than those for poly (DL-lactide) MW 9,000, (-11.07 to -12.21 compared with -10.2 to -10.67), thus confirming that poly (DL-lactide-co-glycolide) is a little less soluble than poly (DL-lactide). The gradients of the lines on these two graphs are approximately the same, indicating the solubility of these materials will increase at the same rate as the density of carbon dioxide is increased.

For comparison, log solubility was plotted against density for lactic acid, Figure 5.9. While straight lines were obtained, as expected from earlier work, it is noted that both the intercept and the gradient vary with temperature. With the polymers, only the intercept varied with temperature, with the gradient remaining constant for each material.

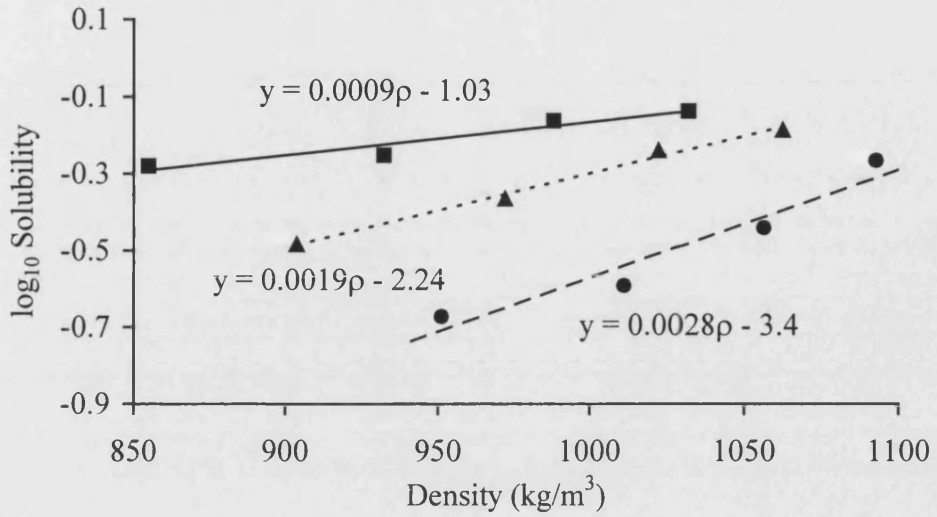



**Figure 5.9.** The variation in solubility of Lactic acid with density of carbon dioxide at temperatures:

—■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C.

From Figure 5.9 it is seen that the intercept for the isotherm at 55°C is significantly greater (less negative) than that for 45°C, which in turn is greater than that at 35°C. this demonstrates that at lower densities, solubility is greatest at higher pressures, as already seen. It is also seen that the gradient of the isotherms is reduced as the temperature increases. This indicates the rate of increase in solubility at higher temperatures with increasing density is less than that at lower temperatures. Hence at sufficiently high densities (ie pressures) the isotherms will cross, showing that solubility will be higher at lower temperatures.

As shown in Figure 5.7, the density of carbon dioxide tends towards a maximum value as the pressure is increased. It is therefore unlikely that the density will get sufficiently high for the isotherms shown on Figure 5.9 to cross.

## 5.7. Physical Changes of the Polymers

### 5.7.1. Materials Collected in the Cold Trap

For most of the polymers studied, the material retained in the cold trap was in the form of a powder, and this was expected from the literature. As early as 1880, Hannay and Hogarth (1880) noted that when the pressure of a solution of supercritical ethylene and iodine was reduced, iodine powder was formed. More recently considerable work has been done investigating the RESS (Rapid Expansion of Supercritical Solutions) process (Tom and Debenedetti, 1991a). This process is used to produce fine powders of materials which are otherwise difficult to divide, for example pharmaceuticals and explosives. RESS exploits the fact that when the pressure of a supercritical solution is reduced, a powder is formed. Tom and Debenedetti (1991b) noted that by varying the conditions such as temperature, pressure and pressure drop, particles of different sizes, shapes and size distribution could be formed.

From the particle size measurements presented in Section 4.6.1 it is seen that poly (DL-lactide) was reduced in size from particles greater than 500μm to particles with an average size of 75μm. The standard deviation of the particles produce was large, at 69μm, and therefore there was a large range of particle sizes produced. This is probably because the supercritical solution was expanded in an uncontrolled manner over a needle valve. Chang and Randolph (1989) describe using laser drilled capillaries of known dimensions to expand solutions to produce defined powders with a small deviation from the mean.

The only soluble polymer studied which did not form a powder in the cold trap was Eudragit® RL100. This formed larger particles, which were collected at the bottom of the cold trap. It is not known why this was. It is possible that the throttle valve was at a temperature greater than the melting point of Eudragit® RL100. On reducing the pressure the Eudragit® RL100 would form a viscous liquid which would tend to adhere to the exit of the valve until a large quantity had built up , before being carried into the cold trap by the flow of carbon dioxide. This is possible as the solubility

measurements with Eudragit® RL100 were carried out at a higher temperature than those for other polymers studied. The melting point of Eudragit® RL100 is not known.

It was noted during the solubility experiments that occasionally large quantities of Eudragit® RL100 were collected in the cold trap. This was different in appearance to the particles usually collected, being white, soft and porous. It is assumed that as well as the carbon dioxide dissolving the polymer, the polymer also dissolved the carbon dioxide, causing it to swell and form a mobile phase. Some of this swollen material was clearly carried over to the cold trap by the flow of carbon dioxide in the rig. From Ehrlich (1992) it is known that polymers often dissolve supercritical fluids and hence swell in their presence, and this behaviour has been described in Section 2.6.

This phenomenon of swollen polymer being carried over into the cold trap was seen a number of times with Eudragit® RL100 as the solute, but was only observed once with poly (DL-lactide), MW 9,000, and was not observed at all with any of the other materials studied. It may have been that these materials do not swell in the presence of carbon dioxide in the same way as did Eudragit® RL100. Alternatively, as most of the materials studied were expensive and only available in small quantities, only approximately 10g poly (DL-lactide), MW 2,000 and 5g poly (DL-lactide), MW 9,000, and poly (DL-lactide-co-glycolide) were used for the solubility experiments. It is quite possible that these materials may have swelled in the presence of carbon dioxide, but there was insufficient present for any to be carried over into the cold trap.

### 5.7.2. The Nature of the Polymer Residues in the Cell

As discussed above, it is thought that the Eudragit® RL100 dissolved carbon dioxide at the supercritical conditions used, and hence swelled and became mobile. Further evidence for this was seen in the residue left in the equilibrium cell following solubility experiments, as described in Section 4.7.1. Here it was noted that the granular starting material had changed to give a homogeneous cylinder of polymer.

Evidence that swelling had taken place was seen as the ballotini at the bottom, and glass wool plug at the top of the cell became incorporated into the cylinder. The results of the swelling experiments, presented in Section 4.7.1, give some insight into the swelling process. From Experiment 3, run for only 3 minutes it was seen that the swelling does not take place instantaneously. All other experiments were run for 60 or 90 minutes, and produced fully swollen, homogeneous cylinders of Eudragit® RL100.

It was also seen that the excessively high pressure and temperatures used for the first three experiments are not required in order to produce porous swollen polymers. Experiment 5 was carried out at conditions close to the critical conditions for carbon dioxide, (the critical pressure and temperature for carbon dioxide is 73.8 bar and 31.1°C). It can therefore be concluded that this swelling will take place in the presence of supercritical carbon dioxide at all conditions of temperature and pressure.

On inspecting the residues in the equilibrium cell there was no visible evidence to show that poly (DL-lactide) or poly (DL-lactide-co-glycolide) swelled in the presence of supercritical carbon dioxide. As noted in the preceding section, only a small amount of these materials were placed in the equilibrium cell, mixed with ballotini, at the start of a series of experiments. It may have been that these materials did swell, but there were not sufficient of them present in the cell for this to be noticeable. Swollen poly (DL-lactide), MW 9,000, was thought to be carried over into the cold trap on one occasion, but this evidence on its own is not conclusive that swelling did take place.

# Chapter 6. Modelling

As noted in Section 2.5, it is desirable to be able to predict solubilities of materials in supercritical fluids. From Chapter 3 it is apparent that the experimentation required to measure this data is expensive both in terms of equipment and time. The ability to predict solubilities to a reasonable degree of accuracy would mean that new compounds could be quickly and cheaply screened in order to assess their suitability to be processed using supercritical fluids. This could potentially lead to the discovery of many new uses for supercritical fluids.

As shown in Chapter 5, it is possible to express the solubility of the polymers studied as a function of the density of the supercritical fluid using an expression of the form described by Robin and Vodar (1953):

$$\log_{10} m = A + B\rho \qquad (6.1)$$

$m$ = solubility (weight basis)

$\rho$ = density of gas

$A$, $B$ = constants

The use of a correlation such as this is valuable, as it reduces the number of experiments which are required in order to fully characterise the solubility of a polymer in a supercritical fluid. The disadvantage is that the constants $A$ and $B$ are unique to each polymer/supercritical fluid system and have to be determined experimentally.

For most pharmaceutically important polymers, very little if any thermodynamic information is available. Very often only an estimate of the molecular mass of the polymer, together with details of the monomer or monomers used is known. Ideally, a method for predicting solubility in a supercritical fluid which requires only this information is required.

## 6.1. Theory

To date most methods to predict the solubility of small molecules in supercritical carbon dioxide have been based on the equality of fugacities, as described in Section 2.5. In this section it was demonstrated that the solubility of a solute in a high pressure gas could be calculated using:

$$y_i = \left(\frac{P_{VPi}}{P}\right)\left(\frac{1}{\Phi_i}\right)\exp\left[\frac{V_i^s}{RT}(P - P_{VPi})\right] \qquad (6.2)$$

$P_{VPi}$ = Vapour pressure of solute

$P$ = System pressure

$\Phi_i$ = Fugacity coefficient of solute in solution

$V_i^s$ = Molar volume of solute

$R$ = Gas constant

$T$ = System temperature

In order to use this expression to calculate solubilities, the vapour pressure and the molar volume of the solute must be known, along with the fugacity coefficient of the solute in solution. While vapour pressure and molar volume data is available for well known materials such as naphthalene, it is not available for the majority of polymers. This information was therefore estimated as described in Appendix C. The fugacity coefficient ($\Phi_i$) is the only term in equation 6.2 which relates to the fact that there are two components present. This can be calculated using a mixture equation of state, which are described in detail in the following section.

### 6.1.1. Cubic Equations of State

In this work the Peng Robinson (PR), (Peng and Robinson, 1975) and Soave Redlich Kwong (SRK), (Soave, 1972) cubic equations of state were used to calculate fugacity coefficient. The Panagiotopoulos-Reid and Simsci modification to both the PR and SRK equations of state were also considered (Simsci, 1997).

Most cubic equations of state are expressed by the following equation (Reid *et al.*, 1986):

$$P = \frac{RT}{V-b} - \frac{a}{V^2 + ubV + wb^2} \qquad (6.3)$$

Where a, b, u and w are defined as shown in Table 6.1.

**Table 6.1.** Constants for equations of state used (Reid *et al.*, 1986)

| Equation | u | w | A | b |
|---|---|---|---|---|
| SRK | 1 | 0 | $\frac{0.42748R^2T_c^2}{P_c}[1+f\omega(1-T_r^{1/2})]^2$ where: $f\omega = 0.48+1.574\omega-0.176\omega^2$ | $\frac{0.08664RT_c}{P_c}$ |
| PR | 2 | -1 | $\frac{0.45724R^2T_c^2}{P_c}[1+f\omega(1-T_r^{1/2})]^2$ where: $f\omega = 0.37464+1.54226\omega-0.26992\omega^2$ | $\frac{0.0778RT_c}{P_c}$ |

$\omega$ is the acentric factor and characterises both the geometry and the polarity of a molecule. It is defined as follows (Reid *et al.*, 1986)

$$\omega = -\log P_{VPi}(\text{at } T_r = 0.7) - 100 \qquad (6.4)$$

For well studied materials, the acentric factor is known. For less well studied materials, this can be estimated as described in Appendix C.

The equations of state as presented above can only be used to calculate the properties of pure materials. In order to calculate the properties of a mixture, including fugacity coefficients mixing rules must be applied. For the SRK and PR equations of state the following mixing rules were used to calculate a and b (Simsci, 1997):

$$a = \sum_i \sum_j x_i x_j a_{ij} \tag{6.5}$$

$$b = \sum_i x_i b_i \tag{6.6}$$

where

$$a_{ij} = (1 - k_{ij})(a_i a_j)^{1/2} \tag{6.7}$$

$k_{ij}$ = binary interaction parameter

The Panagiotopoulos-Reid and Simsci modification to both the PR and SRK equations of state (Simsci, 1997) is in effect a modification to Equation 6.7, such that it becomes:

$$a_{ij} = (a_i a_j)^{1/2}\left[(1 - k_{ij}) + (k_{ij} - k_{ji})\left(\frac{x_i}{x_i + x_j}\right)^{C_{ij}}\right] \tag{6.8}$$

For the general cubic equation of state (Equation 6.3) with the standard mixing rules as described by Equations 6.5-6.7, the following expression for the fugacity coefficient, $\Phi_i$ can be derived, (Reid *et al.,* 1986):

$$\ln\Phi_i = \frac{b_i}{b}(Z-1) - \ln(Z - B^*) + \frac{A^*}{B^*\sqrt{u^2 - 4w}}\left(\frac{b_i}{b} - \delta_i\right)\ln\frac{2Z + B^*(u + \sqrt{u^2 - 4w})}{2Z + B^*(u - \sqrt{u^2 - 4w})} \tag{6.9}$$

where:

$$Z = \frac{PV}{RT} \qquad \text{(Compressibility factor)} \tag{6.10}$$

$$A^* = \frac{aP}{R^2T^2} \tag{6.11}$$

$$B^* = \frac{bP}{RT} \tag{6.12}$$

### 6.1.2. Predicting Polymer Properties Using the Method of Joback

As shown above, critical property data along with the vapour pressure and acentric factor for the polymer in question was required in order to calculate its solubility in supercritical carbon dioxide. In order to predict the critical properties, the method of Joback was used (Joback and Reid, 1987, Reid *et al.*, 1986, Simsci, 1997). This is a development of the Lydersen method, first published in 1955, in which properties are calculated from contributions of the various functional groups which make up a molecule.

In order to use the Joback method, the monomer making up the polymer in question is divided up into functional groups, chosen from tables available in the literature (for example, Joback and Reid 1987). Where there is more than one set of functional groups which can make up the monomer, the set containing the lowest number of different groups is selected. The number of monomer units making up a polymer molecule is calculated using the average molecular mass of the polymer, and the number of each functional group is multiplied up accordingly. Simsci (1997) have extended the work of Joback in order to cover a wider range of functional groups.

The functional group properties can be obtained from tables in the literature. These values are then used to calculate the required critical properties. Once the critical properties of the polymer were known, the acentric factor and vapour pressure could be calculated as described in Appendix C.

## 6.2. Method; The Use of Pro/II

Due to the complex and iterative nature of the calculations to be performed, it was decided to use the chemical engineering modelling package Pro/II (Version 5.0), from Simsci Ltd, Stockport, UK. This is a powerful software package designed to model chemical plant including reactors, distillation columns, flash drums and heat exchangers. Pro/II has an extensive data bank of physical properties, including data for carbon dioxide, naphthalene and lactic acid. It also has the facility to use the

Joback method to predict physical property data. Simsci have increased the number of functional groups which may be used with this method, and all the functional group properties are available in its data bank. A disadvantage with Pro/II is its inability to recognise the supercritical state. This problem was overcome as described below.

In performing the modelling, the components (carbon dioxide and the solute of interest) were specified. Where physical property data was available in the Simsci data bank, this was used, unless noted in the text. In other cases, the functional groups making up the solute were specified, in order that the program could calculate the required data using the Joback method as described in Appendix C. The equation of state to be used was also specified.

The system was modelled as a three phase (two liquids, one vapour) flash drum, in which the temperature and pressure was specified. As noted above, Pro/II was not able to distinguish the supercritical phase, and hence this was predicted as either a vapour or a liquid, depending on the temperature and pressure. When the supercritical phase was predicted as a liquid, it was assumed to be the liquid phase containing the highest concentration of carbon dioxide. In all cases, some carbon dioxide was predicted to be dissolved in the solute. It was occasionally necessary to increase the amount of carbon dioxide in the feed to the flash drum in order to obtain a predicted supercritical phase.

## 6.3. Naphthalene

As naphthalene is a well characterised material, the physical properties required have been determined experimentally, and were available in the Simsci data bank. The solubility of naphthalene was predicted at temperatures 45 and 55°C, and at a range of pressures from 100 to 400 bar to allow comparison with the data of Tsekhanskaya *et al.* (1964). The four equations of state described in Section 6.1 were considered, the Peng Robinson (PR), the Panagiotopoulos-Reid and Simsci modified PR, the

Soave Redlich Kwong (SRK) and the Panagiotopoulos-Reid and Simsci modified SRK.

### 6.3.1. Peng Robinson and Modified PR Equations of State

The results of the modelling using both the standard and modified PR equation of state, and a comparison with experimental data are shown in Figure 6.1 below.

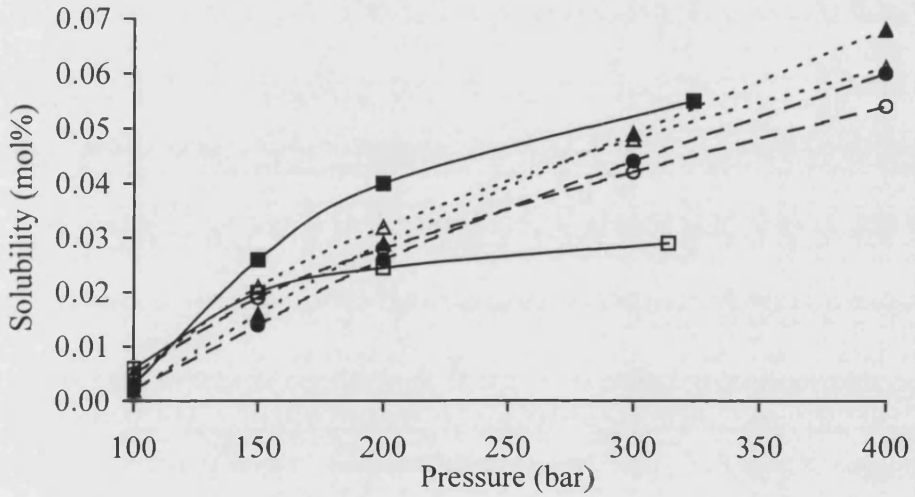



**Figure 6.1.** Solubility isotherms for naphthalene in carbon dioxide:

—■—, —□— Experimental data (Tsekhanskaya *et al.*, 1964)

- -▲- - -, - -△- - - Predicted by the PR equation of state

—●— - -, —○— - - Predicted by the modified PR equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

The predicted solubilities, using both the PR and modified PR equation, show the same general trend as the experimental data gained by Tsekhanskaya *et al.*, (1964), i.e. an increase in solubility with increasing pressure. From the experimental isotherms it is seen that at low pressures, solubility is higher at the lower temperature considered, 45°C. The isotherms cross at a pressure of ~110 bar hence at pressures above this solubility is higher at the higher temperature, 55°C. The solubility isotherms predicted by both the PR equations of state also show this trend, but cross

at higher pressures; 250 bar and 275 bar for the PR and modified PR equations of state respectively.

Experimental data shows that the effect of pressure is more marked at the higher temperature. The experimental isotherm at 45°C seems to be tending towards a maximum at higher pressures, whereas solubility increases more noticeably at 55°C. this trend is not seen in the predicted isotherms, where solubility increases rapidly with pressure over the full range of pressures and temperatures studied. A result of this is the predicted isotherms do not diverge at higher pressures as seen with the experimental isotherms.

The effect of the Panagiotopoulos-Reid and Simsci modifications to the PR equation of state was to reduce the magnitude of the solubilities predicted by a small amount. This was true over the full range of pressures studied. The tends seen for both the PR and modified PR equations of state are the same.

At the pressures considered, 100-400 bar, the predicted solubility isotherms are of the correct order of magnitude, and display some of the trends seen from the experimentally determined solubility isotherms. The effect of temperature on solubility is not predicted well, particularly at higher pressures. At higher pressures, the experimental and predicted isotherms diverge, and hence the predictions become less satisfactory.

### 6.3.2. Soave Redlich Kwong and Modified SRK Equations of State

The results of the modelling using both the standard and modified SRK equation of state together with experimental data are shown in Figure 6.2 below.

The SRK and modified SRK equations of state predicted the same trends as did the PR equation of state. The pressure at which the SRK predicted isotherms cross is 230 bar, closer to the cross over in the experimental isotherms (110 bar) than that predicted by the PR equation of state. The SRK equation of state also underestimates the effect of temperature on the solubility of naphthalene. At 400 bar, a 10°C

increase in temperature is predicted to give an increase in solubility of only 0.004 mol%, compared with the experimentally observed increase of 0.024 mol%, with the same increase in temperature but at the lower pressure of 300 bar.

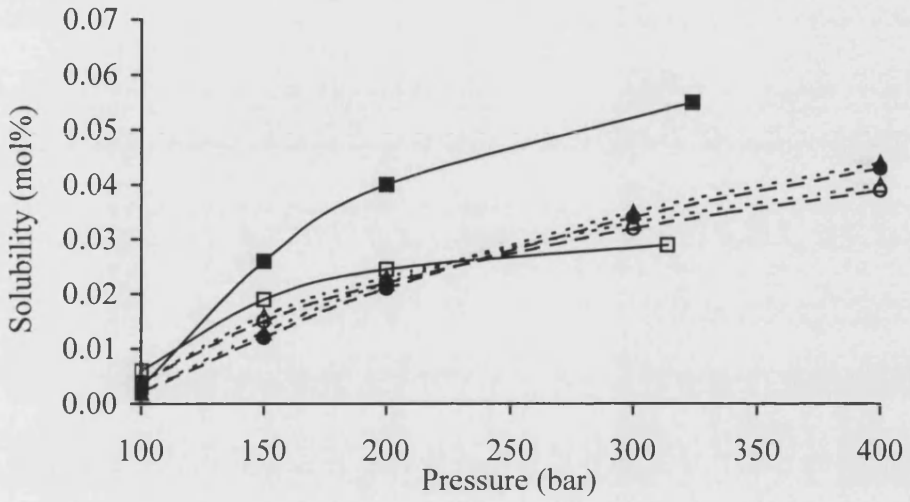



**Figure 6.2.** Solubility isotherms for naphthalene in carbon dioxide:

—■—, —□— Experimental data (Tsekhanskaya *et al.*, 1964)

- -▲- - -, - -△- - - Predicted by the SRK equation of state

—●— - , —⊖— - Predicted by the modified SRK equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

From inspection of Figure 6.1 and Figure 6.2, it is seen that the solubilities predicted by the Peng Robinson equation of state are closer to the experimental values than those predicted by the Soave Redlich Kwong equation. As was seen with the PR equation of state, the modification of Panagiotopoulos-Reid and Simsci has no effect on the shape of the predicted isotherms, it merely reduces all values of solubility predicted in both cases.

It may be fortuitous that the temperatures and pressures selected gave rise to predictions close to the experimental data. At higher temperatures and pressures it is likely that the predicted data will be less satisfactory.

## 6.4. Lactic Acid

Lactic acid, like naphthalene, is well characterised, and all the required physical property data were available in the Simsci data bank. These were used to generate the data plotted in Figure 6.3 and Figure 6.4. In order to test the Joback method of estimating physical properties, the modelling was repeated using only the functional groups making up lactic acid, with no reference to the Simsci data bank. This data is presented in Figure 6.7 and Figure 6.8. In both cases the same equations of state, the Peng Robinson (PR), (Peng and Robinson, 1975), the Panagiotopoulos-Reid and Simsci modified PR, the Soave Redlich Kwong (SRK), (Soave, 1972) and the Panagiotopoulos-Reid and Simsci modified SRK were used.

### 6.4.1. Model Using Simsci Data

#### 6.4.1.1. Peng Robinson and Modified PR Equations of State

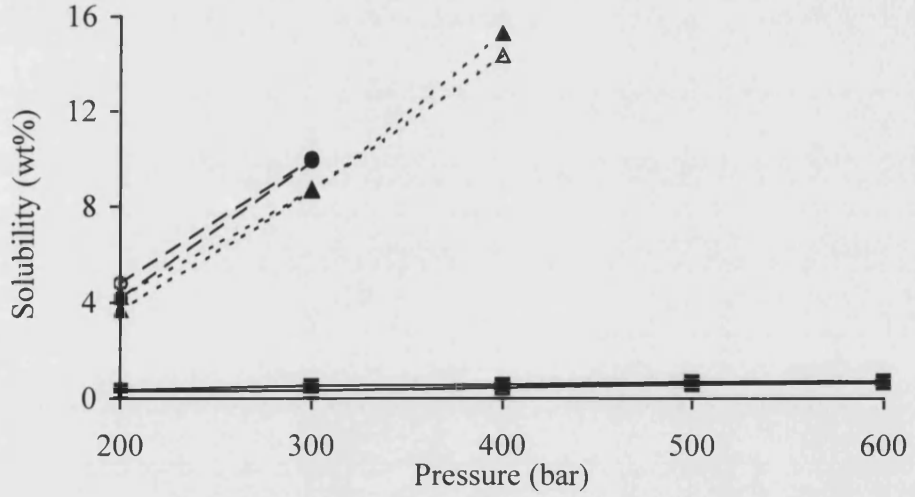



**Figure 6.3.** Solubility isotherms for lactic acid in carbon dioxide:

—■—, —□— Experimental data

- -▲- - -, - -△- - - Predicted by the PR equation of state

—●— - , —○— - Predicted by the modified PR equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

From Figure 6.3 it is seen that the predicted solubility of lactic acid is approximately two orders of magnitude greater than that measured experimentally. From Figure 4.7, it was seen that the solubility of lactic acid increases with increasing pressure and temperature over the range of conditions studied. The predicted solubilities all show the expected trend of increasing considerably with increasing pressure. A rise in pressure of 100 bar is predicted to give an increase in solubility of approximately 6 wt%.

The effect of temperature is more complex. The isotherms predicted using the PR equation of state cross at a pressure of approximately 300 bar, and this is not the case with the experimental isotherms which do not cross. At the lowest pressure considered, 200 bar, solubility was predicted to be higher at 45°C than 55°C, although only by ~0.45 wt%. This was reversed at the higher pressure of 400 bar.

It should be noted that at a pressure of 500 bar (PR equation of state) and 400 bar (modified PR equation of state) the model predicts that the lactic acid becomes completely miscible with the supercritical carbon dioxide, and forms one phase only. Hence it is predicted that the system reaches its upper critical solution pressure (UCSP), a phenomenon discussed in Section 2.6.

The Panagiotopoulos-Reid and Simsci modification has the effect of increasing the solubility predicted, and hence decreasing the pressure at which the UCSP is reached. The shapes of the isotherms predicted by both equations of state are essentially the same.

#### 6.4.1.2. Soave Redlich Kwong and Modified SRK Equations of State

The trends seen for the predictions using the SRK equation of state (Figure 6.4) are the same as those discussed above for the PR equation of state. The magnitude of the solubilities predicted is approximately two orders of magnitude higher than that seen experimentally. It is noted that the solubilities predicted by the SRK equation of state are a little lower than those predicted by the PR equation. The UCSP is

predicted to be at a pressure of between 400 and 500 bar by both the SRK and modified SRK equations of state.

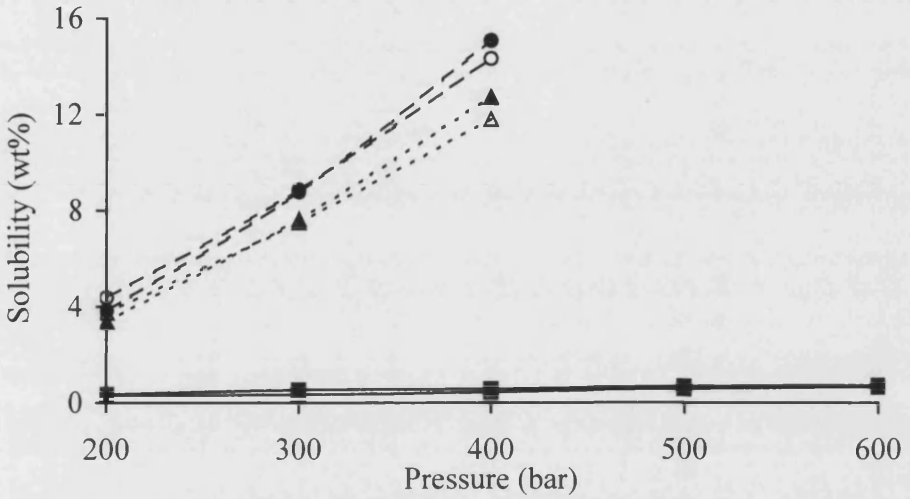



**Figure 6.4.** Solubility isotherms for lactic acid in carbon dioxide:

—■—, —□— Experimental data

- - ▲ - - -, - - △ - - - Predicted by the SRK equation of state

— ● — - , — ⊖ — - Predicted by the modified SRK equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

The effect of increasing pressure is, as expected, to increase the solubility predicted. The effect of temperature predicted by the SRK equation of state is the same as that predicted by the PR equation. The isotherms cross at approximately 300 bar, and hence at pressures below this, increasing the temperature is predicted to decrease the solubility, while at pressures above this the reverse is seen. The effect of the Panagiotopoulos-Reid and Simsci modification to the SRK equation of state is similar to that noted for the PR equation. The modification increases the solubility predicted at all temperatures and pressures but has little effect on the shape of the isotherms.

### 6.4.2. Model Using Data Estimated by the Joback Method

The structure of lactic acid is as shown in Figure 6.5 below. Two functional groups were chosen, as shown in Figure 6.6, to represent the molecule. These functional

groups were specified in Pro/II which then used the Joback method in order to estimate all the physical property data in order to run the model, and hence predict solubility. None of the data on lactic acid in the Simsci data bank was used.

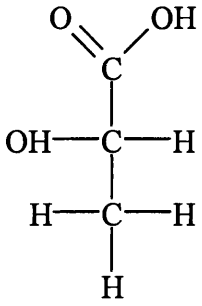



**Figure 6.5.** Lactic acid molecule

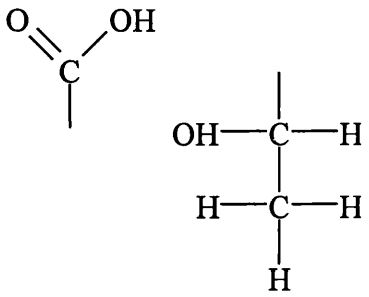



**Figure 6.6.** Functional groups for lactic acid

6.4.2.1. Peng Robinson and Modified PR Equations of State

Figure 6.7 shows the solubility isotherms predicted using the PR and modified PR equations of state are plotted together with the experimental isotherms for comparison.

Both the PR and modified PR equations of state considerably over-estimate the solubility of lactic acid in supercritical carbon dioxide, when using the physical properties of lactic acid predicted by the Joback method. There is little difference between the predictions made by the two equations of state. At the lowest pressure and temperature considered, 200 bar and 45°C, the predicted solubility is 0.72% compared with the experimental value of 0.31%. As the pressure increases the predicted and experimental isotherms diverge, such that at 600 bar and 45°C the predicted solubility is 4.6%, compared to the experimentally determined value of 0.65%.

The isotherms cross at a pressure of approximately 325 bar, hence the model predicts the same trends as were the case for naphthalene (Figure 6.1); at lower pressures solubility increases with decreasing temperature. This was not seen in practice,

solubility always increased with increasing temperature at all pressures from 200 to 600 bar.

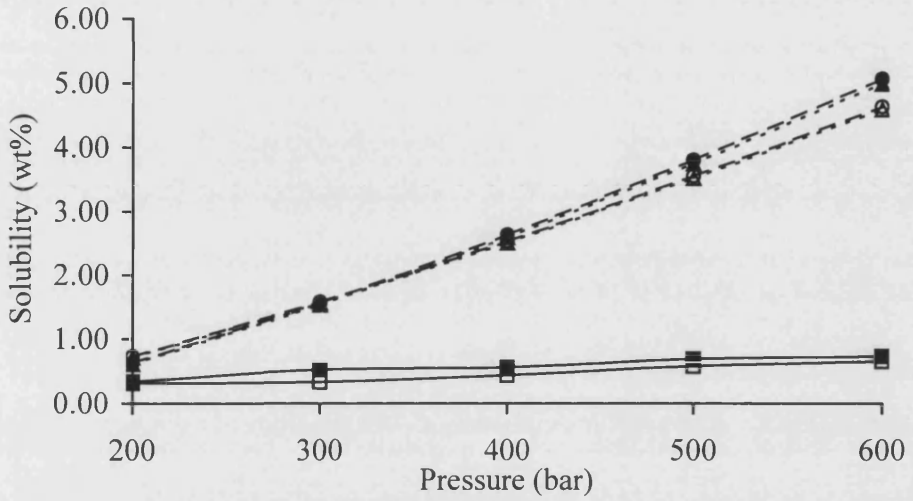



**Figure 6.7.** Solubility isotherms for lactic acid in carbon dioxide, using data estimated with the Joback method:

—■—, —□— Experimental data

- - ▲ - - , - - △ - - Predicted by the PR equation of state

— ● — - , — ⊖ — - Predicted by the modified PR equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

6.4.2.2. Soave Redlich Kwong and Modified SRK Equations of State

From Figure 6.8 it is seen that the SRK and modified SRK equations of state also considerably over-estimate the solubility of lactic acid in supercritical carbon dioxide, but not by as much as the PR equation. The predicted isotherms also cross at a pressure of approximately 325 bar, and hence show the same trends as those generated with the PR equation of state (Figure 6.7).

All the predictions presented for lactic acid considerably over estimate the solubility of lactic acid in supercritical carbon dioxide. It is known that the equations of state employed in this modelling work are best applied to non-polar systems, although the Panagiotopoulos-Reid and Simsci modifications are supposed to improve accuracy in

more polar systems. It was noted in Section 5.4 that the measured solubility of lactic acid in supercritical carbon dioxide was very much lower than expected, especially when compared to that of poly (DL-lactide), MW 2000. This was thought to be due to the fact that lactic acid is a polar material, which forms strong hydrogen bonds, and hence will not tend to be solubilised by a non-polar solvent such as carbon dioxide. It is therefore recommended that the solubility of a polar solute in a non-polar supercritical solvent should not be predicted using these techniques.

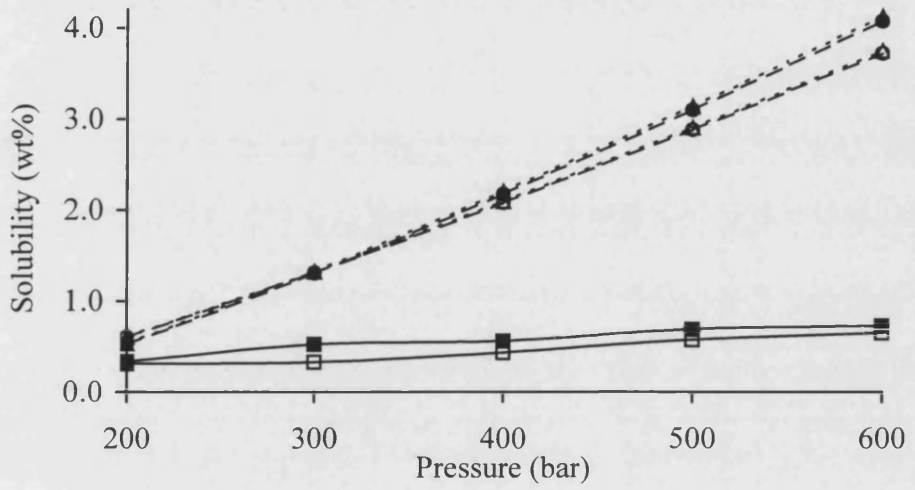



**Figure 6.8.** Solubility isotherms for lactic acid in carbon dioxide, using data estimated with the Joback method:

—■—, —□— Experimental data

--▲---, --△--- Predicted by the SRK equation of state

—●—, —⊖— Predicted by the modified SRK equation of state

Filled symbols, 55°C, Unfilled symbols, 45°C.

When compared to the predictions using the Simsci data, the use of the Joback method to generate physical property data seems to lead to predictions which are closer to the experimental values. This is a potentially misleading result. The data on lactic acid from the Simsci data bank is experimental data, and is expected to be reliable. The Joback method will only estimate physical properties of a compound based on the functional groups making up that compound, and hence is intrinsically less reliable than experimental data. It is hypothesised that the errors in estimating the physical property data partially compensate for the errors introduced when using

the equations of state to predict solubilities, and hence the predictions are closer to the experimental data than would otherwise be seen.

## 6.5. Poly (DL-lactide)

Of the polymers examined experimentally, (Sections 4.2, 4.3, 4.5), poly (DL-lactide) MW 2,000 was selected to be modelled using the techniques described above. As there is no data physical property data available on this material, the Joback method was used to estimate the required data. The structure of the lactide monomer which makes up poly (DL-lactide) is as shown in Figure 6.9.

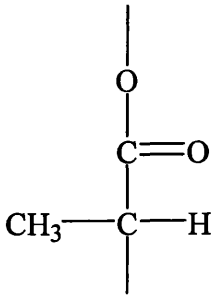


**Figure 6.9.** Lactide monomer

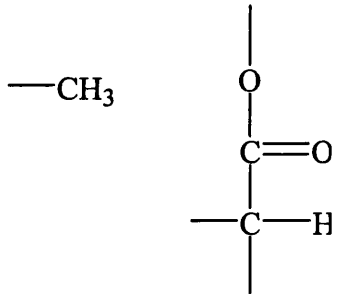


**Figure 6.10.** Functional groups for lactide monomer

This was divided into two functional groups, shown in Figure 6.10. To achieve a molecular weight of approximately 2,000, there must be on average 28 monomer units in each polymer molecule. Due to limitations in the software used (Pro/II), however, only 13 of each functional group could be specified. Therefore the solubility of poly (DL-lactide) MW 936 was predicted in supercritical carbon dioxide. The same equations of state were used as discussed previously, the Peng Robinson (PR), the Panagiotopoulos-Reid and Simsci modified PR, the Soave Redlich Kwong (SRK) and the Panagiotopoulos-Reid and Simsci modified SRK.

### 6.5.1. Peng Robinson and Modified PR Equations of State

The solubilities shown in Figure 6.11 are plotted on a log scale, in order that the variation in solubility with pressure could be observed. The experimental data for poly (DL-lactide) MW 2,000 was not plotted. Since the solubility of poly (DL-lactide) MW 2,000 was in the range of 0.2 – 1 wt%, (Figure 4.1) this could not be displayed satisfactorily on Figure 6.11. The data predicted using the PR equation of state only has been presented: that predicted by the modified PR equation of state has been omitted for clarity as they were almost identical.

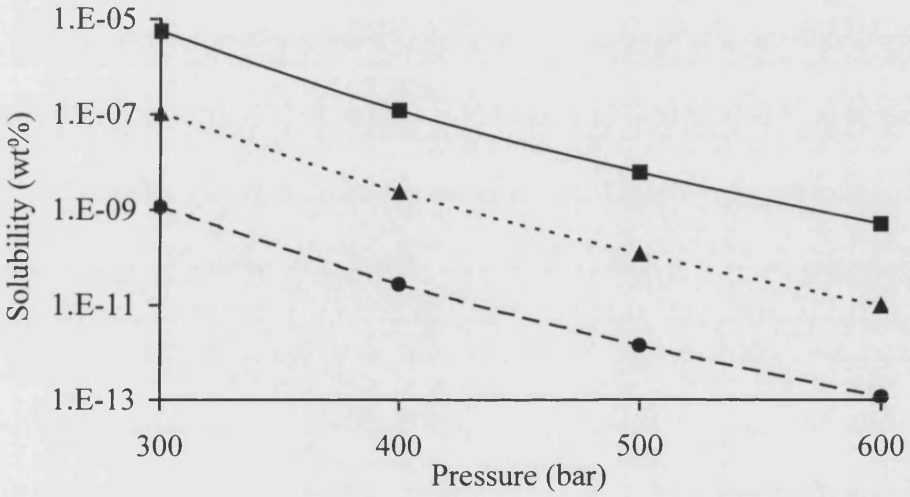



**Figure 6.11.** Solubility isotherms for poly (DL-lactide), MW = 936 in carbon dioxide predicted using the PR equation of state at temperatures: —■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C

It is noted with this large molecular weight material that the solubilities predicted are extremely low and many orders of magnitude lower than those measured experimentally. It is also noted that there is a fundamental error in the model: it predicts that solubility decreases with increasing pressure, something which was not seen with any of the polymers studied experimentally. The effect of both pressure and temperature on the predicted solubility is large, with an increase in 10°C giving rise to an increase in solubility of approximately 2 orders of magnitude. An increase in pressure of 100 bar however is predicted to decrease solubility by approximately

an order of magnitude. It is thought that if it had been possible to increase the MW to 2000, this would have had the effect of reducing the predicted solubility further.

### 6.5.2. Soave Redlich Kwong and Modified SRK Equations of State

The predicted solubilities for poly (DL-lactide), MW 936 using the SRK equation of state are presented in Figure 6.12 below. Again, the results obtained using the modified SRK equation of state have been omitted for clarity, as they are almost identical to those obtained with the SRK equation. A log axis has also been used to highlight the trends.

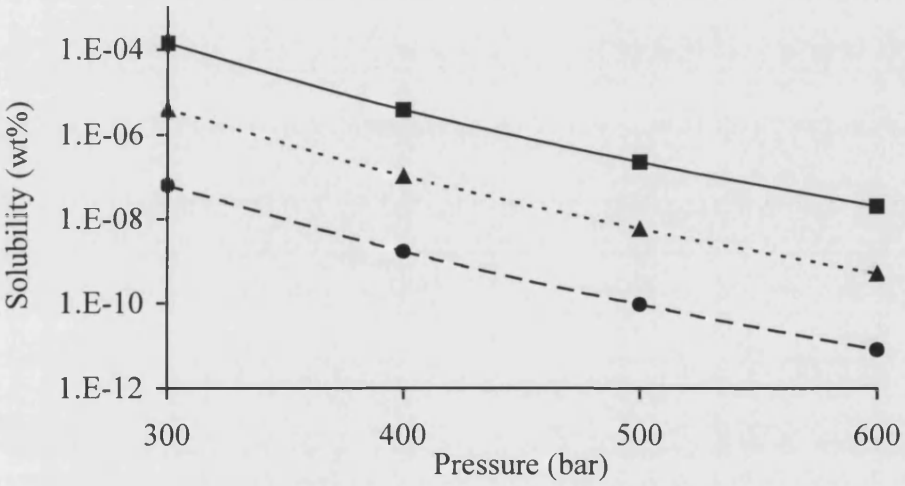



**Figure 6.12.** Solubility isotherms for poly (DL-lactide), MW = 936 in carbon dioxide predicted using the SRK equation of state at temperatures: —■— 55°C, - - ▲ - - - 45°C, — ● — - 35°C

The predicted isotherms from the SRK equation of state show the same trends as those obtained from the PR equation. An increase in pressure has the effect of decreasing the solubility measured, with an increase of 100 bar leading to an order of magnitude reduction in solubility. Temperature has the opposite effect, with a 10°C rise predicted to give an increase in solubility of a little under two orders of magnitude. The solubilities predicted by the SRK equation of state are higher than

those predicted by the PR equation at all the conditions studied, by approximately an order of magnitude.

The predicted solubilities of poly (DL-lactide), MW 936, in supercritical carbon dioxide are disappointing, especially since it was seen that the solubility of naphthalene in supercritical carbon dioxide was predicted well. Both naphthalene and poly (DL-lactide) are reasonably non-polar, and they both have high solubilities in supercritical carbon dioxide compared with more polar materials considered. It is thought that the problem lies with the Joback method, used to estimate the properties of poly (DL-lactide), and hence an alternative method to characterise polymers is required.

Due to the poor results obtained when attempting to predict the solubility of low molecular weight poly (DL-lactide), together with the problems associated with the computer package used, no further work was carried out on the other polymers studied experimentally.

# Chapter 7. Future Work and Conclusions

## 7.1. Scope of Supercritical Carbon Dioxide as a Pharmaceutical Solvent

The principle conclusion to be drawn from this work, which was by its very nature a preliminary investigation, is that supercritical carbon dioxide does not have the potential to become a universal solvent for the application of tablet coatings. Most of the materials tested are simply not soluble enough in supercritical carbon dioxide for it to be considered as a broad spectrum solvent.

As was noted in Section 5.1, a typical batch of 10,000 tablets would require approximately 200g of coating material. It would require literally tonnes of carbon dioxide in order to solubilise this mass of hydroxypropylmethylcellulose (HPMC), for example, and hence the costs involved would be several orders of magnitude greater than current methods. Further, materials such as HPMC can be applied as a water based suspension, overcoming the environmental and possible health risks of using hydrocarbon and chlorinated hydrocarbon solvents. Although these aqueous systems have their problems, such as increased drying times, reduced coating quality, and possible degradation of the active drug compounds, the cost of using them is very low and hence they will continue to be widely used.

Supercritical carbon dioxide is more likely to be used successfully and economically as a solvent for more exotic higher value pharmaceutical excipients which cannot be dissolved in water; applying enteric or controlled release coatings for example. Poly (DL-lactide) is an example of a material which has the potential to be used in controlled release applications, and costs 2-3 orders of magnitude more than HPMC. The solubility of poly (DL-lactide) MW 2,000 in carbon dioxide at 600 bar and 55°C was a little over 1 wt%. In the example discussed above, the typical batch of tablets would require 20 kg of carbon dioxide to solublize sufficient poly (DL-lactide) to coat them. This is not an unduly large amount, especially as it is intended that the carbon dioxide used is recompressed and recycled. This may, with further research, prove to be economically viable.

It is worth considering two coating regimes using supercritical carbon dioxide to evaluate which may be the most economical. The first regime requires the least

amount of carbon dioxide, but has high compression costs. This involves simply reducing the pressure of the supercritical solution down to atmospheric in order to deposit a coating. All the coating material which was dissolved in the carbon dioxide is used, but the recycled carbon dioxide would require compressing from atmospheric pressure to 600 bar in order to be re-used. Compressing a gas is expensive both in terms of capital equipment and energy required.

The second regime uses more carbon dioxide but the recompression costs are lower as the pressure of the supercritical solution is reduced only sufficiently to deposit the majority, but not all of coating material from solution. From the solubility results for poly (DL-lactide), presented in Section 4.2, it is seen that reducing the pressure from 600 bar to 300 bar gives a 5 fold reduction in solubility at 55°C, from 1 wt% to 0.2 wt%. Therefore if the pressure of a solution of poly (DL-lactide) in carbon dioxide at 600 bar is reduced to 300 bar, 80% of the poly (DL-lactide) dissolved therein would come out of solution. In this case the typical batch of tablets referred to above would now require 25 kg of carbon dioxide to apply the coating. The recovered carbon dioxide could be recompressed by cooling to liquefy, pumping the liquid to a pressure of 600 bar, and then re-heating it to obtain a supercritical fluid. As it is far cheaper to pump a liquid than it is to compress a gas, this is likely to result in a considerable saving over the first regime considered.

If supercritical carbon dioxide is to be evaluated for use as a solvent for pharmaceutical polymers, considerably more work is required in the field of predicting the solubility of these materials in carbon dioxide. As was discussed in Chapter 6, determining this type of data experimentally is both expensive and time consuming. There is a large range of polymeric materials of interest to the pharmaceutical industry, and it would be impractical to measure the solubility of them all experimentally.

From Chapter 6 it was seen that the use of the widely known Soave Redlich Kwong, and Peng Robinson equations of state predicted solubility isotherms of the correct shape and order of magnitude for a non-polar, low molecular weight material such as naphthalene. With the polar solute, lactic acid, however the predicted solubility

isotherms were one to two orders of magnitude higher than those measured experimentally. From these results it may have been expected that this method would have predicted the solubility of the reasonably non-polar poly (DL-lactide) in supercritical carbon dioxide with some degree of accuracy. This was unfortunately not the case.

It was therefore shown that these equations of state may be used to obtain initial estimates of the solubility of small, non-polar materials in carbon dioxide, where physical property data is available for the material. These equations of state should not be used to predict the solubility of polar materials or polymers in supercritical carbon dioxide.

## 7.2. Film Formation with Supercritical Carbon Dioxide

Observations made during the solubility experiments made clear that all the polymers studied were collected as particles; either large ones in the case of Eudragit® RL100, or fine powders in the case of poly (DL-lactide) and poly (DL-lactide-co-glycolide). Under the conditions of these experiments therefore, it would not be possible to simply spray a supercritical solution of a polymer onto a batch of tablets in order to coat them since the polymer would form particles rather than a film coating. Thus comprehensive further work is required to study the effects of varying the conditions at which the polymer precipitates. Such effects were not studied since on collecting the solubility data, the pressure of the supercritical solution was reduced rapidly to atmospheric over a valve, in order to collect all the solute. It is possible that reducing the pressure by a smaller amount could alter the characteristics of the particles produced, and may even lead to the formation of a polymer film rather than particles.

Future work to examine these effects may be undertaken using the same experimental rig but with a modification to allow the effects of reducing pressure by a smaller amount to be investigated. The line from the throttle valve would need to be directed into a vessel, the pressure of which was maintained at a predetermined level using a back pressure regulating valve. A target plate could be held in this vessel, below the

line from the throttle valve, to collect samples of the polymer produced for analysis. If this expansion vessel were heated, or placed in a second oven the effect of temperature on the expansion could also be investigated.

## 7.3. The Use of Co-solvents to Increase Solubility

One of the polymers considered in this study, poly (DL-lactide) MW 2,000, has a solubility in excess of 1 wt% in supercritical carbon dioxide at 600 bar and 55°C, and hence warrants some further investigation. The other materials studied, including higher molecular weight poly (DL-lactide), poly (DL-lactide-co-glycolide), and Eudragit RL100 were far less soluble, suggesting that supercritical carbon dioxide is not a suitable solvent, and precluding further investigation. A number of workers in this field (Kurnik and Reid, 1982; Dobbs *et al.,* 1986) have however reported that by mixing a small amount of co-solvent with supercritical carbon dioxide, the solubility of many materials can be enhanced by up to an order of magnitude (Section 2.4.3). Typical co-solvents investigated include polar and non-polar hydrocarbons such as acetone, ethanol and octane. From the details given by these workers, the principle of 'like dissolving like' seems to hold for co-solvents, with polar co-solvents greatly enhancing the solubility of polar solutes, and *vice versa.*

It is recommended that further work be conducted using supercritical carbon dioxide containing small amounts of an appropriate co-solvent, to measure any enhancement in solubility. For poly (DL-lactide-co-glycolide), a polar co-solvent having the ability to form hydrogen bonds, such as ethanol, is recommended. It was thought that the reason poly (DL-lactide-co-glycolide) was less soluble than poly (DL-lactide) was due to the presence of strong hydrogen bonds in the former material.

In order to quantify any enhancement of solubility with a co-solvent, further modifications would be required to the rig and the experimental procedure. If the co-solvent is miscible with liquid carbon dioxide, and this is certainly the case with small quantities of ethanol, a mixed feed can be prepared in a suitable pressure vessel, by adding known masses of co-solvent and carbon dioxide. Once mixed, this

can be used in the same way as the standard carbon dioxide cylinders described in Section 3.1.3. An alternative method to obtain a mixed supercritical fluid feed to the rig would be to use a high pressure metering pump to supply the co-solvent at a known rate. The carbon dioxide and co-solvent would be mixed in the preheat coil, prior to entering the equilibrium cell. In order for this method to be acceptable, the flow rate of carbon dioxide must be measured accurately. Precautions would need to be taken to prevent the co-solvent from condensing out in the cold trap, which would lead to erroneously high solubilities being measured. The trap would need to be maintained at a higher temperature than was used in this work and it may be necessary to pass dry nitrogen through the cold trap at the end of each experiment, but prior to weighing in order to remove any co-solvent remaining therein.

While at first sight the use of hydrocarbon co-solvents would appear to be contrary to the environmental aims of this project, it should be borne in mind that only a small amount of co-solvent would be used; less than 5 wt% in carbon dioxide. This still represents a significant reduction in the amount of hydrocarbons required, and hence the quantity released into the atmosphere. Further if carbon dioxide with a co-solvent were to be used in a commercial coating process, there would be considerable scope for recycling. As noted earlier it would not be necessary to reduce the pressure of the system to atmospheric in order to cause the coating material to precipitate. The solvent would be maintained above the critical pressure of carbon dioxide in order to allow it to be easily liquefied by reducing the temperature by a small amount. This liquid could then be pumped back up to high pressure and reused in a closed circuit, hence a small amount of carbon dioxide and co-solvent could be used to apply a coating to a large batch of tablets.

### 7.3.1. Film Formation with Co-solvents

It was noted previously (Section 7.2) that when the pressure of a carbon dioxide/polymer solution is released the polymer precipitates out as particles or a powder rather than a film which would be necessary for a tablet coating system. In Section 7.1, the possibility of reducing the pressure of the solution by a smaller

amount, rather than down to atmospheric was discussed in the hope that this may lead to the formation of films rather than powders. Should this not be successful, an alternative method to produce films will need to be found. It is possible that the presence of a co-solvent will have benefits further to those of enhancing the solubility of the coating material i.e. a co-solvent may improve the film forming properties.

In Section 2.7.6 it was noted that the paint industry is conducting research into the area of replacing some of the hydrocarbon solvents in spray paints with supercritical carbon dioxide in an attempt to reduce VOC emissions. Traditionally, spray painting has required the use of a mixture of solvents. Some have been light, volatile and with a low viscosity to enable the paint solution to be atomized in the spray gun. These generally evaporate rapidly before the paint droplets hit the target and so some heavier, less volatile solvents are included. These allow the paint droplets to run together on the surface being painted to form a continuous coating, and evaporate more slowly. It has been discovered by Busby *et al.* (1990) that the lighter solvents can be replaced with supercritical carbon dioxide, which leads to a large reduction in the amount VOCs released. The heavier solvents are still required in order to obtain a satisfactory coating.

It is probable that the same principles will hold true in the area of coating pharmaceuticals. When the pressure of a supercritical solution is reduced the solute is likely to precipitate almost instantaneously, and would not have time to form a film; hence the powders observed in the experiments. The presence of a less volatile solvent such as a co-solvent is likely to encourage the formation of either larger particles, or if a correctly designed jet is used, a film coating.

### 7.3.2. Co-solvent Residues

While this is a strong case for using hydrocarbon co-solvents, the residue which may remain on the tablets is a cause for concern. While the principle driving force for conducting this research is an environmental one, a secondary aim was to eliminate

the possibility of potentially harmful hydrocarbon residues remaining on the tablets following the coating process. During the course of the experiments it was seen that the solubility of most of the polymers studied in supercritical carbon dioxide was very low, but it is accepted that most hydrocarbon solvents are either soluble in or miscible with supercritical carbon dioxide to a high degree. Therefore if a co-solvent were used, the flow of supercritical carbon dioxide should aid the evaporation and removal of the co-solvent from the coating. This, coupled with the fact that far less hydrocarbon solvent is required in a supercritical system than a conventional one, should result in less hydrocarbon residue remaining on the tablets.

## 7.4. Drying using Supercritical Carbon Dioxide

An obvious development which leads from the discussion in Section 7.3.2 is to use supercritical carbon dioxide as a drying medium, or an antisolvent, rather than a solvent for applying pharmaceutical coatings, a development analogous to that of the GAS (gas anti solvent) method for producing defined particles. From the discussion in Section 2.7.4, it was seen that the GAS method was developed to overcome the problem of low solubilities which restricted the use of the RESS (rapid expansion of supercritical solutions) method of producing particles.

In RESS, the target material is dissolved in a supercritical fluid, usually carbon dioxide. This solution is then expanded, i.e. the pressure reduced, and the material precipitates to produce the desired particles. The disadvantage of this method is that the material in question must be soluble in the supercritical fluid, which often is not the case. To overcome this problem, GAS was developed. In this method, the material of interest is dissolved in a suitable solvent, usually a hydrocarbon, and sprayed into a vessel containing supercritical carbon dioxide. As the solvent rapidly dissolves in the carbon dioxide, the target material precipitates out in the form of particles.

It is proposed to apply the coating to the tablets using a conventional hydrocarbon solvent. The solvents can then be removed using a stream of supercritical carbon

dioxide at moderate temperature and pressure (say 35°C and 100 bar), rather than using warm air to dry the tablets. Provided the correct amount of carbon dioxide is used, the resulting solution is likely to be reasonably concentrated in the hydrocarbon solvent. As the pressure of the supercritical carbon dioxide/hydrocarbon mixture is reduced, the hydrocarbon can be recovered with minimal expense for reuse. Currently, the hydrocarbons dried from the tablets with warm air are either vented and lost, or are partially recovered by cooling the drying air, at considerable expense.

Most of the coating materials studied have a low solubility in supercritical carbon dioxide, and so bring this into contact with ready coated tablets will have little effect on the permanence of the coating. It is accepted that supercritical carbon dioxide has a high diffusivity. The swelling experiments carried out with Eudragit® RL100 show that carbon dioxide at a moderate temperature and pressure can be adsorbed in a matter of minutes by relatively large granules of polymer. Carbon dioxide should therefore penetrate the thin film coating deposited on the tablets quickly, rapidly removing virtually all the hydrocarbon solvent.

The potential advantages of a supercritical drying system are:

- most of the hydrocarbon solvent used is recovered for reuse, reducing VOC emissions,
- it offers faster processing times,
- it operates at low temperatures (~35°C),
- it does not rely on the coating material being soluble in a particular solvent; any solvent which will dissolve in or mix with supercritical carbon dioxide can be used.

The possible disadvantages are, the effect of the supercritical carbon dioxide on the quality of the coating, and the cost of both the high pressure equipment required, and the energy used in compressing the carbon dioxide. It would not be acceptable for the coating to become permanently swollen and porous, hence this needs to be investigated in detail. The costs of this system should be evaluated, and compared to the current costs (financial and environmental) associated with current drying methods.

## 7.5. Summary of Conclusions

### 7.5.1. Solubility of Polymers in Supercritical Carbon Dioxide

The solubility of a range of pharmaceutical excipients in supercritical carbon dioxide have been measured.

- For all the polymers studied, increasing the pressure of the system increased the solubility.

- For lactic acid, an increase in the temperature of the system led to an increase in the solubility at all pressures studied.

- For low molecular weight polymers, (MW less than 10,000) increasing the temperature at high pressures led to an increase in the solubility. At lower pressures an increase in the temperature had a negligible effect on the solubility.

- Increasing the temperature of Eudragit® RL100, the only high molecular weight polymer studied, had the effect of reducing the solubility at a pressure of 600 bar.

- The solubility of the polymers studied depended on their molecular weights. It was seen in general terms that increasing the molecular weight of a polymer by an order of magnitude had the effect of reducing the solubility by the same amount.

- The solubility of the materials studied depended on their polarity. Polar materials, which were thought to form hydrogen bonds, were less soluble in supercritical carbon dioxide than were non-polar materials.

- The solubility of hydroxypropylmethylcellulose (HPMC) in supercritical carbon dioxide was measured to be 0.008 wt% at 600 bar and 60°C. This is too low to enable supercritical carbon dioxide to be used as an economically viable solvent for processing this material.

- Poly (DL-lactide), of molecular weight 2,000 had a solubility in supercritical carbon dioxide of 1.09 wt% at 600 bar and 55°C. This was the only material studied with a solubility sufficiently high to make further work into the feasibility of using pure carbon dioxide as a solvent for processing excipients economically worth while.

### 7.5.2. Predicting Solubility in Supercritical Carbon Dioxide

- The use of the Soave Redlich Kwong and Peng Robinson equations of state to predict the solubility of naphthalene, a non-polar, low molecular weight solute, in supercritical carbon dioxide gave isotherms of the same order of magnitude and similar shape to those determined experimentally.

- The use of the same equations of state to predict the solubility of lactic acid, a polar solute, in supercritical carbon dioxide gave isotherms approximately two orders of magnitude greater than those determined experimentally.

- When considering poly (DL-lactide), MW 936, the use of the same equations of state, coupled with the Joback method to estimate the physical properties of the solute, predicted solubility isotherms many orders of magnitude less than those measured experimentally for poly (DL-lactide), MW 936. Further, the solubility of poly (DL-lactide), MW 936 was predicted to decrease with increasing pressure.

- While the use of the Soave Redlich Kwong and Peng Robinson equations of state may be used for the initial assessment of the solubility of small non-polar

materials in supercritical carbon dioxide, they should not be used to predict the solubility of polar materials or polymers in supercritical carbon dioxide.

### 7.5.3. Swelling of Polymers by Supercritical Carbon Dioxide

- Observations showed that some of the polymers studied swelled in the presence of supercritical carbon dioxide, to form mobile, polymer rich phases. This certainly occurred with Eudragit® RL100, and was thought to have occurred with poly (DL-lactide), MW 9,000. It is possible that this phenomenon was common to all the polymers used, but no evidence was seen for the low molecular weight materials under test.

- The swelling of Eudragit® RL100 in the presence of supercritical carbon dioxide was not an instantaneous process.

- The swelling of Eudragit® RL100 takes place in the presence of carbon dioxide at all supercritical conditions up to 600 bar and 60°C.

### 7.5.4. Supercritical Carbon Dioxide as a Pharmaceutical Solvent

- It has been shown that supercritical carbon dioxide is not suitable as general pharmaceutical solvent, as the solubility of the majority of polymers tested was extremely low.

- It is thought that supercritical carbon dioxide may be useful for processing high value pharmaceutical materials where the costs of high pressure equipment can be justified. This use will need to be evaluated on a case by case basis.

## References


Andrews, T. (1875) The Bakerian Lecture - On the Gaseous State of Matter. *Proc. Roy. Soc.* **24** 455-457.

Atkins, P.W. (1990) Physical Chemistry. 4th ed p.135 Oxford University Press. Oxford UK.

Banister, J.A., Howdle, S.M. & Poliakoff, M. (1993) Preparative Scale Organometallic Chemistry in Supercritical Fluids. *J. Chem. Soc., Chemical Communications* **24** 1814-1815.

Bonner, D.C. (1977) Solubility of Supercritical Gases in Polymers – A Review. *Polymer Engineering and Science* **17**(2) 65-72.

Boysen, R.L. (1981) High Pressure (Low and Intermediate Density) Polyethylene. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed, Vol 16, pp. 402 - 420. Wiley USA.

BS 5500 (1994) Specification for Unfired Fusion Welded Pressure Vessels 6th Ed BSi.

Busby, D.C., Glancy, C.C., Hoy, K.L., Kuo, A.C., Lee, C. & Nielsen, K.A. (1990) Supercritical Spray Application Technology: A Pollution Prevention Technology for the Future. *Proceedings of the Water Borne and High Solids Coatings Symposium* Mississippi, Feb 21-23 1991. pp. 218-239.

Campbell, R.M. & Lee, M.L. (1985) Semi-preparative Supercritical Fluid Extraction/Fractionation. *Preprints of Papers. American Chemical Society, Division of Fuel Chemistry* **30**(3) 189-194.

Chang, C.J. & Randolph, A.D. (1989) Precipitation of Microsize Organic Particles from Supercritical Solutions. *AIChE Journal* **35**(11) 1876-1882

Chrastil, J. (1982) Solubility of Solids and Liquids in Supercritical Gases *J. Phys. Chem.* **86** 3016-3021.

Crittenden, B. & Kolaczkowski, S. (1995) Waste Minimization A Practical Guide. IChemE. U.K.

Cygnarowicz, M.L., Maxwell, R.J. & Seider, W.D. (1990) Equilibrium Solubilities of β-carotene in Supercritical Carbon Dioxide. *Fluid Phase Equilibria* **59** 57-71.

Department of the Environment (1991) Environmental Protection Act – 1990 – Waste Management – the Duty of Care, a code of practice. HMSO, London, U.K.

Diepen, G.A.M. & Scheffer, F.E.C. (1948) The Solubility of Naphthalene in Supercritical Ethylene. *J. Amer. Chem. Soc.* **70** 4085-4089.

Dobbs, J.M., Wong, J.M. & Johnston, K.P. (1986) Nonpolar Co-Solvents for Solubility Enhancement in Supercritical Fluid Carbon Dioxide. *J. Chem. Eng. Data* **31** 303-308.

Dobbs, J.M., Wong, J.M., Lahiere, R.J. & Johnston, K.P. (1987) Modification of Supercritical Fluid Phase Behavior Using Polar Co-Solvents. *Ind. Eng. Chem. Res.* **26** 56-65.

Edwards, J.H. (1995) Potential Sources of Co2 and the Options for its Large-Scale Utilization Now and in the Future. *Catalysis Today,* **23**(1), 59-66.

Eggers, R. (1978) Large Scale Industrial Plant for Extraction with Supercritical Gases. *Angew. Chem. Int. Ed. Engl.* **17** 751-754.

Ehrlich, P. (1992) Supercritical Polymer Solutions and Polymer-Fluid Interactions at High Pressure. *Chemtracts - Macromolecular Chemistry* **3** 1-19.

Ekart, M.P., Bennett, K.L., Ekart, S.M., Gurdial, G.S., Liotta, C.L. & Eckert, C.A. (1993) Cosolvent Interactions in Supercritical Fluid Solutions. *AIChE Journal* **39**(2) 235-248.

Friedrich, J.P. (1984) The United States of America. Supercritical Carbon Dioxide Extraction of Lipids from Lipid Containing Materials. *US Patent 4,466,923.*

Gallagher, P.M., Coffey, M.P., Krukonis, V.J. & Klasutis, N. (1989) Gas Antisolvent Recrystallization: New process to Recrystallize Compounds Insoluble In Supercritical Fluids. In: Johnston, K.P. & Penninger, J.M.L. (Eds) (1989) Supercritical Fluid Science and Technology. *A.C.S. Symposium Series 406.* pp. 334-354.

Gallagher, P.M., Coffey, M.P., Krukonis, V.J. & Hillstrom W.W. (1992) Gas Antisolvent Recrystallization of RDX: Formation of Ultra-fine Particles of a Difficult to Comminute Explosive. *J. Supercrit. Fluids* **5** 130-142.

Gallagher-Wetmore, P., Coffey, M.P. & Krukonis, V. (1994) Application of supercritical fluids in Recrystallization: Nucleation and Gas Anti-Solvent Techniques. *Respiratory Drug Delivery* **IV** 287-295.

Gaspar, F., Leeke, G.A., Lu, T., Santos, R. & King, M.B. (1997) Extraction of Essential Oils and Other Compounds from Natural Sources using Supercritical Carbon Dioxide: Single Plate Models. In: Reverchon, E. (Ed) (1997) Fourth Italian Conference on Supercritical Fluids and their Applications. Capri, Italy, 7/10 Sept 1997. pp. 209-216.

Giddings, J.C., Myers, M.N., McLaren, L. & Keller, R.A. (1968) High Pressure Gas Chromatography of Nonvolatile Species. *Science* **162** 67-73.

Hannay, J.B. & Hogarth, J. (1880) On The Solubility of Solids in Gases. *Proc. Roy. Soc.* **30** 178-188.

Heller, J.P., Dandge, D.K., Card, R.J. & Donaruma, L.G. (1985) Direct Thickeners for Mobility Control of Carbon Dioxide Floods. *Society of Petroleum Engineers Journal* **25** 679-686.

Iezzi, A., Enick, R. & Brady, J. (1989) Direct Viscosity Enhancement of Carbon Dioxide. In: Johnston, K.P. & Penninger, J.M.L. (Eds.) (1989) Supercritical Fluid Science and Technology. *A.C.S. Symposium Series 406* pp. 122-139.

IRPTC (1992) Dichloromethane *Journal of the International Register of Potentially Toxic Chemicals.* **11**(1 & 2) 30-33.

Iwai, Y., Fukuda, T., Koga, Y. & Arai, Y. (1991) Solubilities of Myristic Acid, Plamitic Acid, and Cetyl Alcohol in Supercritical Carbon Dioxide at 35°C. *J. Chem. Eng. Data* **36** 430-432.

Iwai, Y., Yamamoto, H., Sohda M., Tanaka, Y., Shimizu, T. & Arai, Y. (1989) A Flow Type Apparatus for Measurement of Solubilities of Coal Derived Compounds in Supercritical Fluid. *Mem. Fac. Eng., Kyushu Univ.* **49** 175-183.

Joback, K.G. & Reid, R.C. (1987) Estimation of Pure Component Properties from Group Contributions. *Chem. Eng. Comm.,* **57** 233-243.

Johnston, K.P. & Eckert, C.A. (1981) An Analytical Carnahan-Starling-van der Waals Model for Solubility of Hydrocarbon Solids in Supercritical Fluids. *AIChE Journal* **27** 773-779.

Juni, K. & Nakano, M. (1987) Poly(hydroxy acids) in Drug Delivery. *CRC Critical Reviews in Therapeutic Drug Carrier Systems* **3** 209-232.

Juvinal, R.C. (1983) Fundamentals of Machine Component Design. pp. 288-290 Wiley USA.

Krase, N.W. & Lawrence, A.E. (1946) E.I. du Pont. Process for the Preparation of Ethylene Polymers. *U.S. Patent 2,396,791.*

Kramer, A. & Thodos, G. (1988) Solubility of 1-Hexadecanol and Palmitic Acid in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **33** 230-234.

Kurnik, R.T., Holla, S.J. & Reid, R.C. (1981) Solubility of Solids in Supercritical Carbon Dioxide and Ethylene. *J. Chem. Eng. Data* **26** 47-51.

Kurnik, R.T., & Reid, R.C. (1982) Solubility of Solid Mixtures in Supercritical Fluids. *Fluid Phase Equilibria* **8** 93-105.

Larson, K.A. & King, M.L. (1986) Evaluation of Supercritical Fluid Extraction in the Pharmaceutical Industry. *Biotecnol. Prog.* **2** 73-82.

Madras, G., Erkey, C. & Akgerman, A. (1993) A New Technique for Measuring Solubilities of Organics in Supercritical Fluids. *J. Chem. Eng. Data* **38** 422-423.

Matson, D.W., Fulton, J.L., Petersen, R.C. & Smith, R.D. (1987) Rapid Expansion of Supercritical Fluid Solutions: Solute Formation of Powders, Thin Films, and Fibers. *Ind. Eng. Chem. Res.* **26** 2298-2306.

McHugh, M. & Krukonis, V. (1994) Supercritical Fluid Extraction Principles and Practice. 2nd Ed Butterworths USA.

McHugh, M. & Paulaitis, M.E. (1980) Solid Solubilities of Naphthalene and Biphenyl in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **25** 326-329.

Mendes, R.L., Coelho, J.P. & Ferandes, H.L. (1995) Applications of Supercritical Carbon Dioxide Extraction to Microalgae and Plants. *J. Chem. Tech. Biotechnol.* **62** 53-59.

Michels, A. & Michels, C. (1933) Influence of Pressure on the Dielectric Constant of Carbon Dioxide up to 1000 atm between 25 and 150°C. *Proc. Roy. Soc.* **A151** 409-434.

Michels, A., Michels, C. & Wouters, H. (1935) Isotherms of Carbon Dioxide Between 70 and 3000 atm. *Proc. Roy. Soc.* **A153** 214-224.

Peng, D.Y. & Robinson, D.B. (1975) A New Two Constant Equation of State. *Ind. Eng. Chem. Fundam.* **15**(1) 59-64.

Petersen, R.C., Matson, D.W. & Smith, R.D. (1987) The Formation of Polymer Fibers from the Rapid Expansion of Supercritical Fluid Solutions. *Polymer Engineering and Science* **27** 1693-1697.

Pickard, J.F. & Rees, J.E. (1972) Modern Trends in Pharmaceutical Coating. In: Unit Operations in Tableting Technology. Lucien Charial Memorial Colloquium, 6/9/72, Lisbon.

Porter, S.C., Bruno, C.H. & Jackson, G.J. (1982) Pan Coating of Tablets and Granules. In: Lieberman, H.A. & Lachman, L. (eds) Pharmaceutical Dosage Forms: Tablets. Volume 3. pp. 73-117 Marcel Dekker USA.

Prausnitz, J.M., Lichtenthaler, R.N. & de Azevedo, E.G. (1986) Molecular Thermodynamics of Fluid Phase Equilibria. 2nd Edition. pp. 171-184 Prentice-Hall USA.

Randolph, T.W. (1990) Supercritical Fluid Extractions in Biotechnology. *Trends in Biotechnology* **8** 78-82.

Redlich, O. & Kwong, J.N.S. (1949) On the Thermodynamics of Solutions. *Chem. Rev.* **44** 233-244.

Reid, R.C., Prausnitz, J.M. & Poling, B.E. (1986) The Properties of Gases and Liquids. pp. 42-46, pp. 143-145. M$^{c}$Graw-Hill USA.

Richter, M. & Sovova, H. (1993) The Solubility of Two Monoterpenes in Supercritical Carbon Dioxide. *Fluid Phase Equilibria* **85** 285-300.

Robin, S. & Vodar, B. (1953) Solubility in Compressed Gases. *Discuss. Faraday Soc.* **15** 233-243.

Roselius, W., Vitzhum, O. & Hubert, P. (1974) HAG Aktiengesellschaft. Method for the Production of Caffeine Free Coffee Extract. *US Patent 3,843,824.*

Ruchatz, F., Kleinebudde, P. & Müller, B.W. (1997) Residual Solvents in Biodegradable Microparticles. *Journal of Pharmaceutical Sciences* **86** 101-105.

Seitz, J.A., Mehta, S.P. & Yeager, J.L. (1986) Tablet Coating. In: Lachman, L., Lieberman, H.A. & Kanig, J.L. (Eds) The Theory and Practice of Industrial Pharmacy 3$^{rd}$ Ed. Lea & Febiger USA.

Shigley, J.E. (1986) Mechanical Engineering Design. 4$^{th}$ Ed. McGraw Hill USA.

Simsci (1997) PRO/II Version 5.0 Reference Manual. Simulation Sciences Inc. California, USA.

Smith, R.D. (1986) Battelle Memorial Institute. Supercritical Fluid Molecular Spray Film Deposition and Powder Formation. *US Patent 4,582,731.*

Smith, R.D., Kalinoski, H.T., Udseth, H.R. & Wright, B.W. (1984) Rapid and efficient Capillary Column Supercritical Fluid Chromatography with Mass Spectrometric Detection. *Anal. Chem.* **56** 2476-2480.

Smith, R.D. & Udseth, H.R. (1983) Mass Spectrometry with Direct Supercritical Fluid Injection. *Anal. Chem.* **55** 2266-2272.

Smith, R.D., Udseth, H.R., Wright, B.W. & Yonker, C.R. (1987) Solubilities in Supercritical Fluids: The Application of Chromatographic Measurement Methods. *Sep. Sci. Tech.* **22** 1065-1086.

Soave, G. (1972) Equilibrium Constants for a Modified Redlich-Kwong Equation of State. *Chem. Eng. Sci.* **27** 1197-1203.

Tavana, A., Chang, J., Randolph, A.D. & Rodrigues, N. (1989) Scanning of Cosolvents for Supercritical Fluids Solubilisation of Organics. *AIChE Journal* **35**(4) 645-648.

Tiltscher, H., Wolf, H. & Schelchshorn, J. (1984) Utilization of Supercritical Fluid Solvent Effects in Heterogeneous Catalysts. *Ber. Bunsenges. Phys. Chem.* **88** 897 - 900.

Ting, S.S.T., Macnaughton, S.J., Tomasko, D.L. & Foster, N.R. (1993) Solubility of Naproxen in Supercritical Carbon Dioxide With and Without Co-solvents. *Ind. Eng. Chem. Res.* **32** 1471-1481.

Tom, J.W. & Debenedetti, P.G. (1991a) Formation of Bioerodable Polymeric Microspheres and Microparticles by Rapid Expansion of Supercritical Solutions. *Biotechnol. Prog.* **7** 403-411.

Tom, J.W. & Debenedetti, P.G. (1991b) Particle Formation with Supercritical Fluids. A Review. *J. Aerosol Sci.* **22** 555-584.

Tom, J.W., Lim, G.B., Debenedetti, P.G. & Prud'homme, R.K. (1993) Applications of Supercritical Fluids in the Controlled Release of Drugs. In: Kiran, E. & Brennecke, J.F. (Eds.) (1993) Supercritical Fluid Engineering Science. *ACS Symposium Series 514* pp. 238-257.

Tsekhanskaya, Y.V., Iomtev, M.B. & Mushkina, E.V. (1962) Solubility of Diphenylamine and Naphthalene in Carbon Dioxide Under Pressure. *Rus. J. Phys. Chem.* **36** 1177-1181.

Tsekhanskaya, Y.V., Iomtev, M.B. & Mushkina, E.V. (1964) Solubility of Naphthalene in Ethylene and Carbon Dioxide Under Pressure. *Rus. J. Phys. Chem.* **38** 1173-1176.

Verschueren, K. (Ed) (1983) Handbook of Environmental Data on Organic Chemicals. 2nd Ed. Van Nostrand Reinhold, New York, USA. pp 848-849

Villard, P. (1898) Solution of Solids and Liquids in Gases. *Chemical News* Dec 16th 297-298.

Vukalovich, M.P. & Altunin, V.V. (1965) Thermophysical Properties of Carbon Dioxide. pp. 237-265. Translated from Russian under the direction of the United Kingdom Atomic Energy Authority (1968). Collet's London, UK.

Warzinski, R.P. & Ruether, J.A. (1984) Fractional Destraction of Coal Derived Materials. *Fuel* **63** 1619-1621.

Wilson, R.E., Keith, P.C. & Haylett, R.E. (1936) Liquid Propane - Use in Dewaxing, Deasphalting, and Refining Heavy Oils. *Ind. Eng. Chem.* **28** 1065.

Wurster, D.E. (1953) Wisconsin Alumni Research Foundation. Method of Applying Coatings to Edible Tablets and the like. *U.S. Patent 2,648,609.*

Yau, J.S. & Tsai, F.N. (1992) Solubilities of 1-Hexadecanol and 1-Octadecanol in Subcritical and Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **37** 285-287.

York, P. & Hanna, M. (1996) Particle Engineering by Supercritical Fluid Technologies for Powder Inhalation Drug Delivery. *Respiratory Drug Delivery.* **V** 231-239.

Yu, E., Richter, M., Chen, P., Wang, X., Zhang, Z. & Tavlarides, L.L. (1995) Solubilities of Polychlorinated Biphenyls in Supercritical Carbon Dioxide. *Ind. Eng. Chem. Res.* **34** 340-346.

Zosel, K. (1974) Studiengesellschaft Kohle GmbH, Process for Recovering Caffeine. *U.S. Patent 3,806,619.*

Zosel, K. (1981) Studiengesellschaft Kohle GmbH, Process for the Decaffeination of Coffee. *U.S. Patent 4,247,570.*

## Appendix A. Mechanical Design of Equilibrium Cell

### Equilibrium Cell Specifications

- To be machined from 316 stainless steel bar. The mill certificates for the steel used should be retained, and handed over with the cell, for inspection by National Vulcan.

- All tolerances to be +/- 0.1 mm, except where tighter tolerances are specified on the drawings.

- The tolerances on angles to be +/- 0.5°, except where tighter tolerances are specified on the drawings.

- The fit between the end connectors and the equilibrium cell is critical, as the integrity of the O-ring seals depend on this:

    - The surface finishes are to be 0.4 μm Ra, or better on the mating surfaces between the end connector and the equilibrium cell.

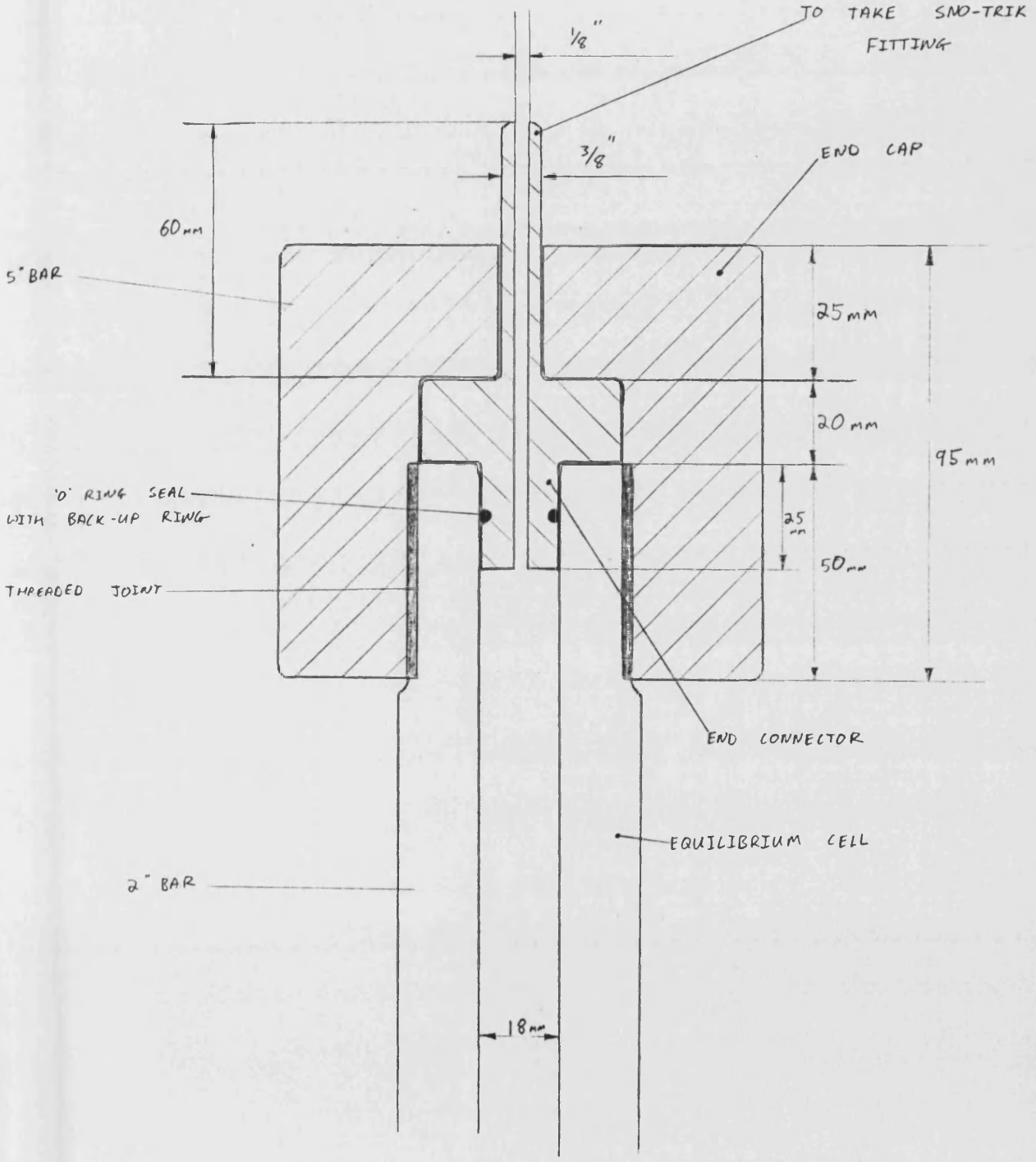
    - The tolerance on the end connector is to be f8, as defined in B.S.4500, i.e. -16 to - 43 μm. (0.707 - 0.708").

    - The tolerance on the equilibrium cell is to be H9, as defined in B.S.4500, i.e. 0 to +43 μm. (0.709 -0.710").

- The dimensions for the grooves on the end connectors are critical. These must be made within the specification on the drawing.

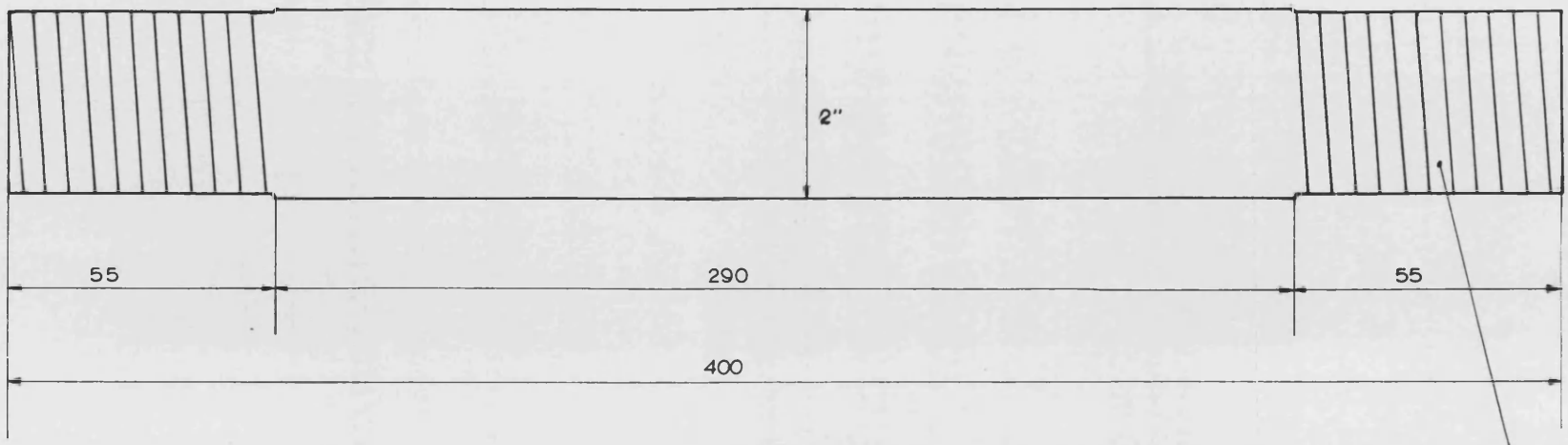
- The $^{3}/_{8}$" tube section on the end connectors are to take standard Autoclave Engineers high pressure fittings. A Sno-Trik reducer was then used to connect into the $^{1}/_{4}$" thick walled tubing used for the bulk of the rig.

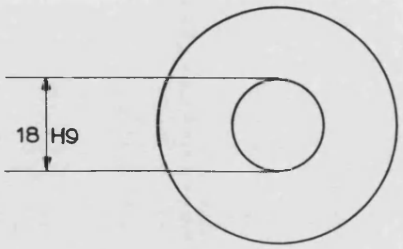
## Manufacturing and General Assembly Drawings.

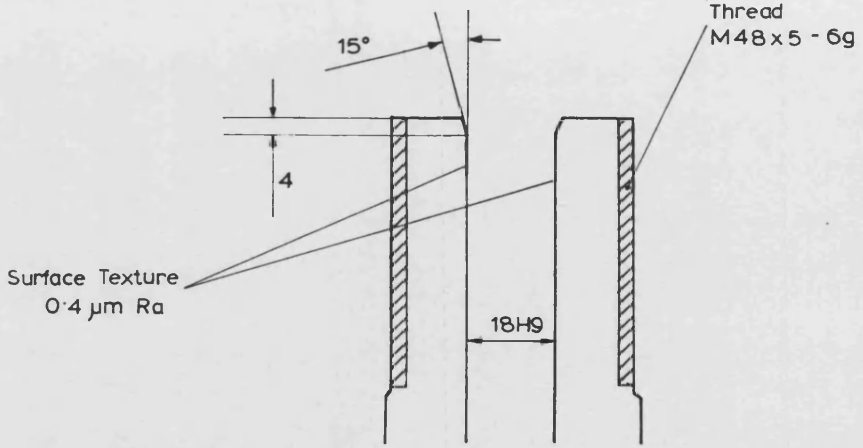



ALL COMPONENTS TO BE MACHINED FROM 316 S.S.

| | | |
|---|---|---|
| 30/11/94 | | DRAWN BY ANDREW BROADBENT |
| | EQUILIBRIUM CELL END CONNECTIONS | UNIVERSITY OF BATH |
| NOT SCALE | | SCHOOL OF CHEMICAL ENGINEERING |

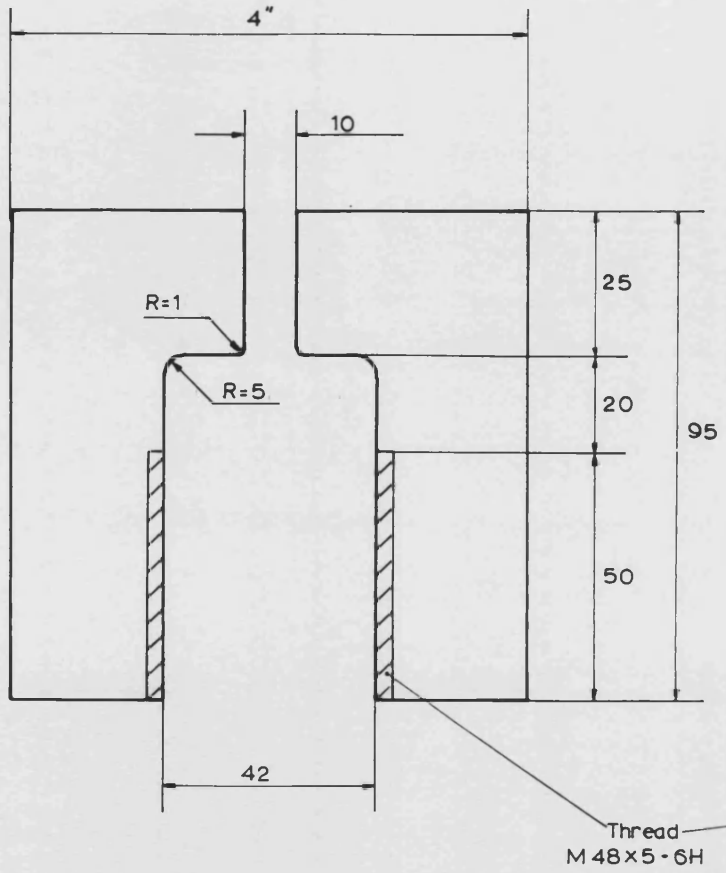


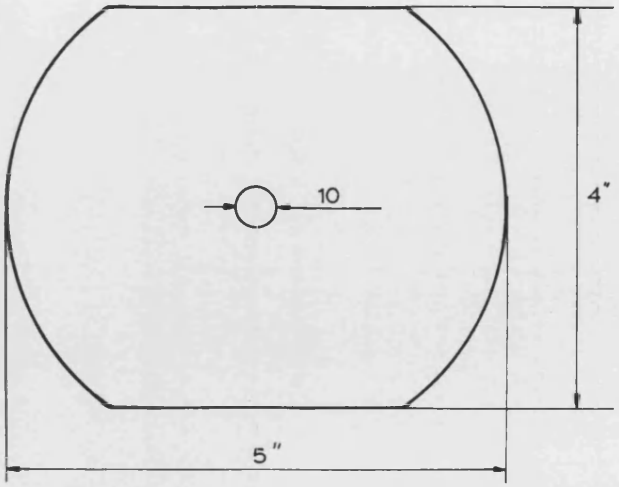




| | | |
|---|---|---|
| 30/1/95 | | ANDREW BROADBENT |
| DIMENSIONS IN: mm | EQUILIBRIUM CELL | UNIVERSITY OF BATH |
| | | SCHOOL OF CHEMICAL ENGINEERING |

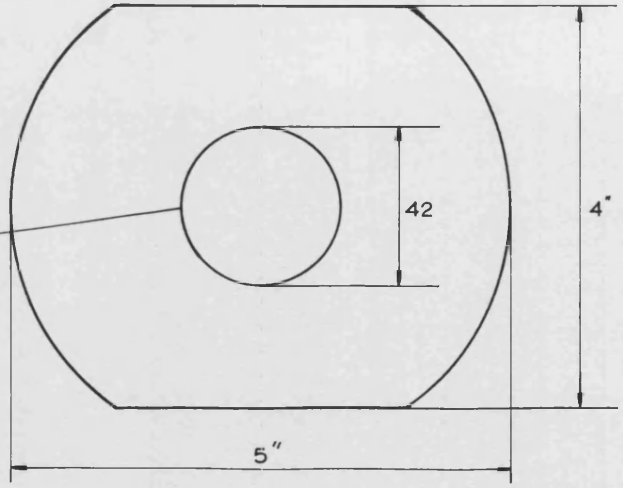
Section



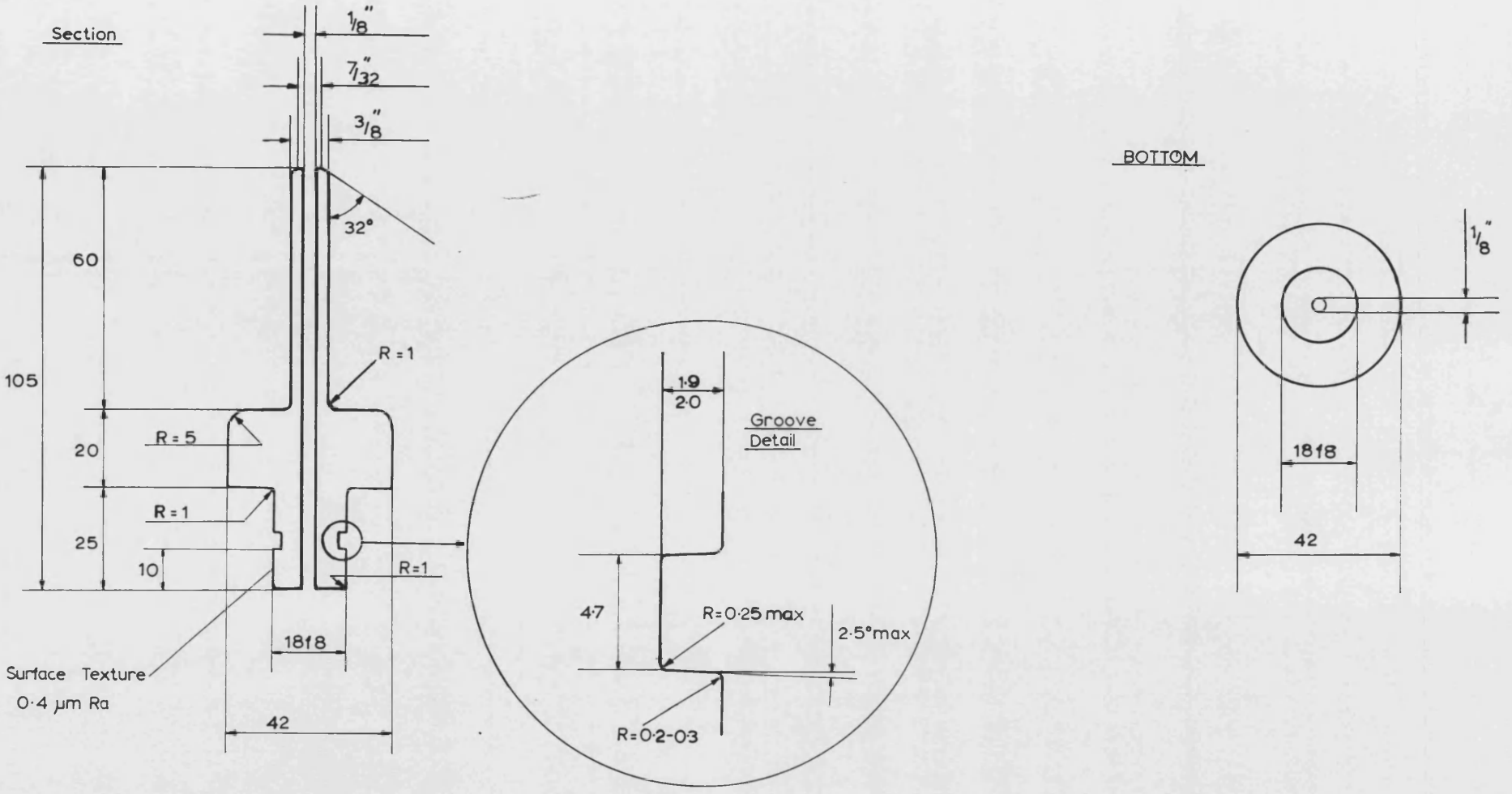

Top




Bottom




| | | |
|---|---|---|
| 31/1/95 | | ANDREW BROADBENT |
| DIMENSIONS: mm | EQUILIBRIUM CELL END CAP. DESIGN 1. | UNIVERSITY OF BATH |
| TOLERANCES: ±0·1 mm | | SCHOOL OF CHEMICAL ENGINEERING |




| | | |
|---|---|---|
| 31/1/95 | | ANDREW BROADBENT |
| DIMENSIONS IN: mm | EQUILIBRIUM CELL END CONNECTOR, DESIGN 1. | UNIVERSITY OF BATH |
| TOLERANCES ± 0·1 mm | | SCHOOL OF CHEMICAL ENGINEERING |

**Design Calculations.**

## 1 Specification.

| | |
|---|---|
| Material of construction, | 316 Stainless Steel, |
| Design pressure | P = 690 bara, (69 $Nmm^{-2}$, 10,000psi) |
| Design temperature | T = 250°C |
| Design stress of steel (BS 5500) | $\sigma_d$ = 103 $Nmm^{-2}$ |

### 1.1 Dimensions of Cell.

$d_i$ = Internal diameter = 18 mm

$l_i$ = Internal length = 350 mm

## 2 Wall Thickness

Applying Lame's equations:

$$-\sigma_r = A - \frac{B}{d^2} \qquad \text{A.1}$$

$$\sigma_\theta = A + \frac{B}{d^2} \qquad \text{A.2}$$

Where:

$\sigma_r$ = radial stress, $Nmm^{-2}$

$\sigma_\theta$ = hoop stress, $Nmm^{-2}$

d = diameter, mm

A, B, = constants of integration.

For thick walled pressure vessels, where $d = d_i$:

$\sigma_r$ = P = 69 $Nmm^{-2}$

$\sigma_\theta$ = max permitted stress $\sigma_d$ 103 $Nmm^{-2}$

Therefore equations A.1 and A.2 become:

$$-69 = A - \frac{B}{18^2} \qquad \text{A.3}$$

$$103 = A + \frac{B}{18^2} \qquad \text{A.4}$$

A.4 – A.3:

$$172 = \frac{2B}{18^2}$$

$$B = 27864\ \text{N}$$

Substitute B into A.4:

$$A = 103 - \frac{27864}{18^2}$$

$$A = 17\ \text{Nmm}^{-2}$$

When d = minimum outer diameter, $d_{om}$, $\sigma_r = 0\ \text{Nmm}^{-2}$, therefore A.1 becomes:

$$0 = A - \frac{B}{d_{om}^2} \qquad \text{A.5}$$

Substitute A and B into A.5 to give:

$$d_{om}^2 = 1639$$

$$d_{om} = 40.5\ \text{mm}$$

The minimum wall thickness, $t_m$, can now be calculated:

$$t_m = \frac{d_{om} - d_i}{2} \qquad \text{A.6}$$

$$t_m = \frac{40.5 - 18}{2}$$

$$t_m = 11.25\ \text{mm}$$

The equilibrium cell is to be cut from 2" (50 mm) bar, giving a wall thickness of 16 mm, thus there is a large margin for safety. The thread has to be taken into account,

as this will reduce the wall thickness of the cell at the ends. The thread size selected is M48 x 5. The minor diameter of this thread is 42 mm, therefore the least wall thickness will be 12 mm, hence greater than the minimum permitted.

## 3 End Sections.

These may fail in one of two ways. The threads may strip, or the end may fracture at the base of the threads.

The force, F, exerted on the end sections due to the pressure within the vessel may be calculated using:

$$P = \frac{F}{A} \qquad \text{A.7}$$

where: A = Cross - sectional area, $= \frac{\pi d_i^2}{4}$

$= 254.5 \text{ mm}^2$

$$F = P * A$$
$$= 69 * 254.5$$
$$= 17561 \text{ N}$$

### 3.1 Thread Stress.

The thread selected is M48 x 5. The major diameter $d_m$ of this thread is 48 mm, and the minor or root diameter $d_r$ is 42 mm (Shigley, 1986).

From Juvinall (1983) thread bearing stress, $\sigma_t$, is calculated using:

$$\sigma_t = \frac{4F}{\pi\left(d_m^2 - d_r^2\right) n} \qquad \text{A.8}$$

Where n = no of threads in contact, (10)

$$\sigma_t = \frac{4 * 17561}{\pi\left(48^2 - 42^2\right) 10}$$

$$\sigma_t = 4.2 \text{ Nmm}^{-2}$$

This is well below the design stress.

### 3.2 End Fracture.

Fracture is most likely to occur at the base of the threads, at the point where the cross-sectional area of steel is least. This will be across the root diameter of the thread. The stress area to be considered, $A_t$, is the area of the annulus with inner diameter $d_i$ and outer diameter $d_r$.

$$A_t = \frac{\pi\left(d_r^2 - d_i^2\right)}{4} \qquad \text{A.9}$$

$$A_t = \frac{\pi\left(42^2 - 18^2\right)}{4}$$

$$A_t = 1130 \text{ mm}$$

The stress in this area, $\sigma_f$, is found using:

$$\sigma_f = \frac{F}{A} \qquad \text{A.10}$$

$$\sigma_f = \frac{17561}{1130}$$

$$\sigma_f = 15.6 \text{ Nmm}^{-2}$$

This is well below the design stress.

**Ansys Models**

Ansys is a powerful finite element analysis package used by engineers for a variety of tasks including the study of structures under load. It is available on the University of Bath computer network under an educational licence agreement. The following analysis was carried out in conjunction with Mr. W. R. Taylor, School of Mechanical Engineering.

The cell end caps, and end connectors were modelled using Ansys as part of the design procedure as no straightforward design protocol was available.

Ansys requires the following to be specified by the user:

- The size and shape of the object.
- The Young's modulus of the material under consideration.
- The position, direction and magnitude of the force acting on the object.
- The point or points at which the object is restrained.

The shapes of both objects were defined by specifying key points, and then joining them up with lines to give two dimensional shapes. These were then rotated about a specified axis to form the desired three dimensional shape.

The Young's modulus for 316 stainless steel at 250°C was taken to be 180E-9 $Nm^{-2}$.

The force acting on the components was calculated from the maximum pressure and the cross sectional area of the cell.

The points of restraint were known from the general assembly drawing.

When run, Ansys divides the shape up into many small elements. The stress distribution within the object is calculated by considering the interactions between the elements caused by the applied force and the restraint. The accuracy of the model depends on the number and size of the elements, and this is specified by the user.

The results are shown as stress distributions in the two dimensional shape initially defined. The stresses are assumed to be the same all round the structure, as it displays rotational symmetry.

**Ansys Program and Results for the End Cap.**

```
C***  end4.dat,  Model of end cap, using 4" od.

/SHOW,X11,,1
/TITLE,PRESSURE CELL END CAP STRESS ANALYSIS
/FILNAM,CELL
/UNITS,SI
/PREP7

ET,1,PLANE82
KEYOPT,1,3,1

K,1,0.0035,0
K,2,0.0508,0
K,3,0.0508,0.098
K,4,0.0225,0.098
K,5,0.0225,0.048
K,6,0.0225,0.029
K,7,0.0035,0.029
K,8,0.0165,0.029

L,1,2
L,2,3
L,3,4
L,4,5
L,5,6
L,6,8
L,8,7
L,7,1

C*** GENERATE FILLET RADIUS
LFILLT,6,5,0.005

C*** CREATE AREA FROM EXISTING LINES AND DEFINE MATERIAL
PROPERTIES

AL,1,2,3,4,5,9,6,7,8
MP,EX,1,180E9

APLOT

C*** DEFINE ELEMENT SIZE

ESIZE,0.0025
MAT,1
AMESH,1
```

```
EPLOT

FINI
/SOLU

C*** VERTICAL CONSTRAINT ON SIDE SURFACE ( LINE 4 )

LSEL,S,LINE,,4
NSLL,S,1
D,ALL,ALL,0.000
NSEL,ALL
LSEL,ALL

C*** LOADING

SFL,7,PRES,30E6

C*** SOLUTION

SOLVE

FINI

/POST1

/PBC,ALL,1
/PNUM,LINE,1
/PSF,PRES,NORM,2
PLNSOL,S,EQV
```

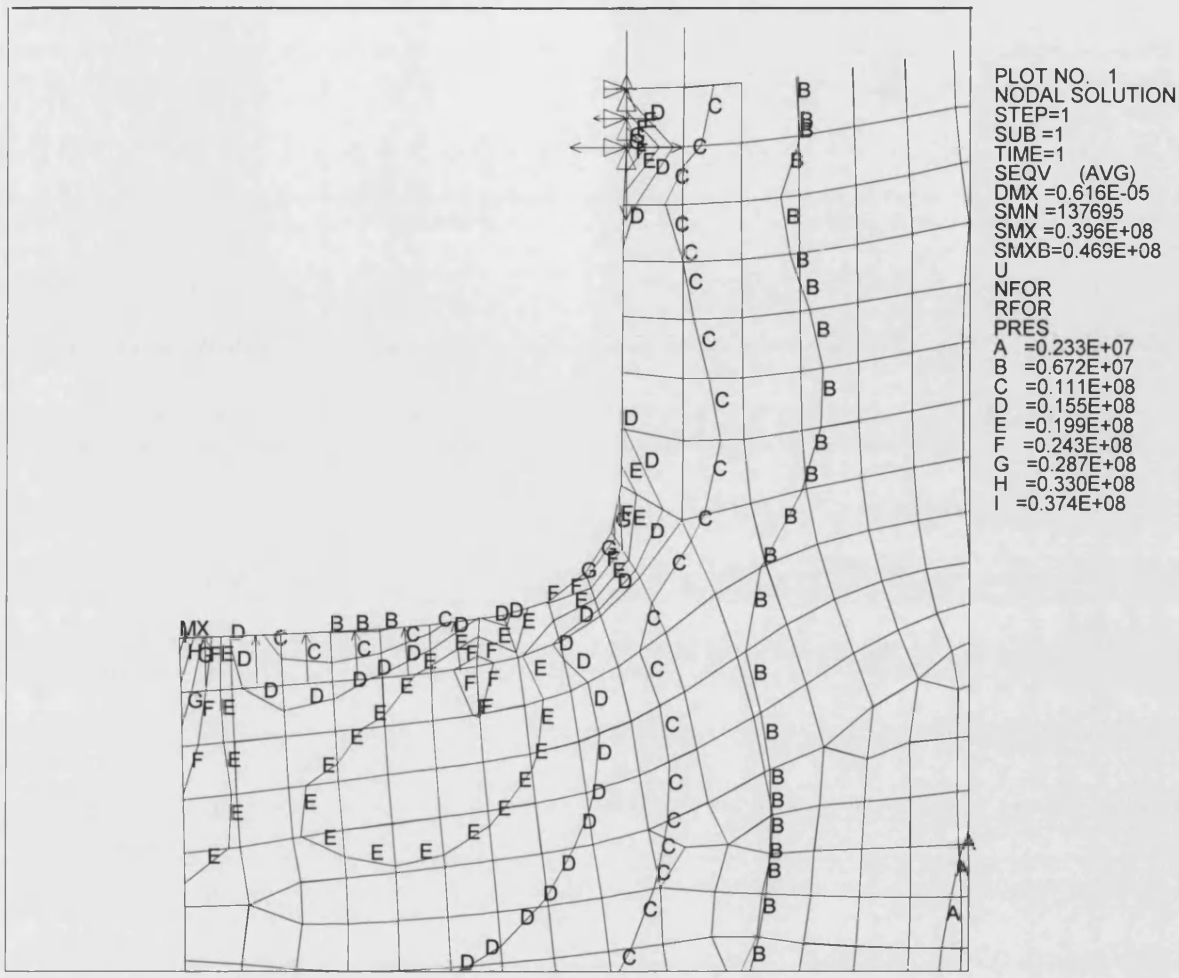



**Figure A5. END CAP STRESS CONCENTRATIONS.**

From Figure A5 it can be seen there is a large stress concentration up to 0.287E8 $Nm^{-2}$ in the internal corner. This is well below the design stress of the steel, 1.03E8 $Nm^{-2}$. A stress concentration was expected here, and hence the corner was designed with a 5mm radius, to reduce the stress.

The model calculated that the largest stress concentration occurs at the point labelled MX in the bottom left hand corner. This was due the load being applied along the whole of that length. The end caps have been made with these corners rounded off eliminating this problem.

The points of restraint are shown by the arrows at the top of the picture, and these correspond to the position of the thread. The stresses calculated at these points are

far higher than the thread stress calculated previously. This is because the model did not take into account the geometry of the threads.

**Ansys Program and Results for the End Connector.**

```
C***  endcon3.dat,  Model of end connector.

/SHOW,X11,,1
/TITLE,PRESSURE CELL END CONNECTOR STRESS ANALYSIS
/FILNAM,CNEC
/UNITS,SI
/PREP7

ET,1,PLANE82
KEYOPT,1,3,1

K,1,0.00159,0
K,2,0.00475,0
K,3,0.00475,0.041
K,4,0.02,0.061
K,5,0.02,0.081
K,6,0.009,0.081
K,7,0.009,0.09
K,8,0.009,0.0913
K,9,0.0068,0.0913
K,10,0.0068,0.096
K,11,0.009,0.096
K,12,0.009,0.106
K,13,0.00159,0.106
K,14,0.00159,0.09

L,1,2
L,2,3
L,3,4
L,4,5
L,5,6
L,6,7
L,7,14
L,14,1
L,7,8
L,8,9
L,9,10
L,10,11
L,11,12
L,12,13
L,13,14

C*** GENERATE FILLET RADII, LINES 16, 17, & 18,

LFILLT,5,6,0.003
LFILLT,10,11,0.00025
```

```
LFILLT,11,12,0.00025

LPLOT,ALL

C*** CREATE AREAS FROM EXISTING LINES AND DEFINE MATERIAL
PROPERTIES

AL,1,2,3,4,5,16,6,7,8,
AL,9,10,17,11,18,12,13,14,15,7
AADD,1,2

MP,EX,1,180E9

APLOT

C*** DEFINE ELEMENT SIZE

ESIZE,0.001
MAT,1
AMESH,3

EPLOT

FINI
/SOLU

C*** HORIZONTAL CONSTRAINT ON LINE 3

LSEL,S,LINE,,3
NSLL,S,1
D,ALL,ALL,0.000
NSEL,ALL
LSEL,ALL

C*** LOADING

SFL,11,PRES,0.6E8
SFL,12,PRES,0.6E8
SFL,13,PRES,0.6E8
SFL,14,PRES,0.6E8
SFL,15,PRES,0.6E8
SFL,10,PRES,0.6E8

C*** SOLUTION

SOLVE

FINI
```

```
/POST1

/PBC,ALL,1
/PNUM,LINE,1
/PSF,PRES,NORM,2
PLNSOL,S,EQV
```

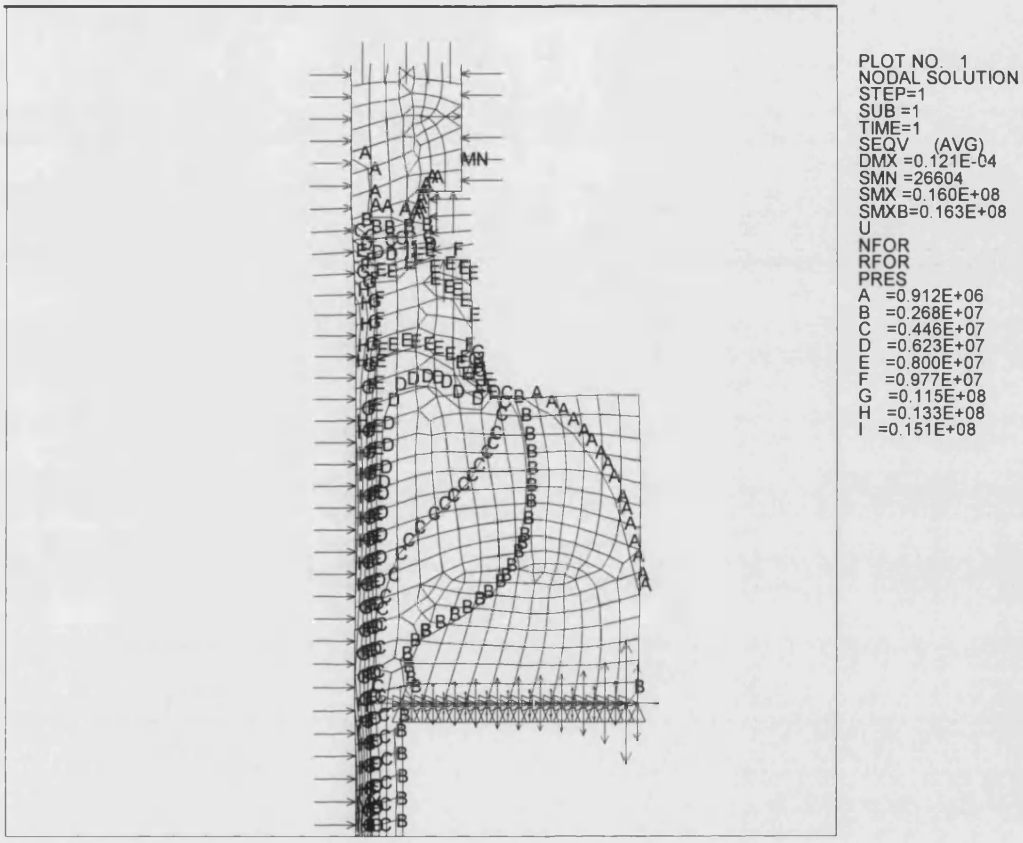



**Figure A6. End Connector Stress Analysis**

From Figure A6 it can be seen that the largest calculated stresses occurred along the left hand side of the picture, i.e. inside the hole through the end connector. The minimum wall thickness permitted for the thin tubular section of the end connector was calculated using Lame's equations, as described previously. This was considerably less than the specified wall thickness, and therefore the model was presumed to be inaccurate at that part.

The highest stress concentrations were expected to occur at the corner just below the groove for the O-ring. The model gave a large stress concentration of 0.115E8 $Nm^{-2}$ at that point, which is well below the design stress of 1.03E8 $Nm^{-2}$.

## Appendix B. Equipment Suppliers

The rig components, as detailed in Section 4.1.3, were purchased from the following suppliers.

| | |
|---|---|
| High pressure pump<br>High pressure valves | George Mellor Limited.<br>Orion Park,<br>Northfield Avenue,<br>Ealing,<br>London.<br>W13 9SJ |
| High pressure fittings | Bristol Valve and Fitting Co. Ltd.<br>Fourth Way,<br>Avonmouth Way,<br>Avonmouth,<br>Bristol.<br>BS11 8DL |
| High pressure tubing | Southampton Tube Sales.<br>Majestic Road,<br>Nursling,<br>Southampton.<br>SO16 0AF |
| Oven<br>Dry gas meter | Fisons Scientific Equipment.<br>Bishop Meadow Road,<br>Loughborough,<br>Leicestershire.<br>LE11 0RG |

| | |
|---|---|
| Pressure and temperature transducers | Endevco UK Ltd.<br>Melbourn,<br>Royston,<br>Herts.<br>SG8 6AQ |
| O-rings and back up rings | Precision Polymer Engineering Ltd.<br>Clarendon Road,<br>Blackburn,<br>Lancs.<br>BB1 9SS |
| Pressure cell testing | Baskerville Ltd.<br>324c Barlow Moor Road,<br>Chorlton-cum-Hardy,<br>Manchester.<br>M21 8AX |
| Pressure cell insurance | National Vulcan Engineering Insurance.<br>St. Marys Parsonage,<br>Manchester.<br>M60 9AP |

## Appendix C. Estimating Physical Property Data

In order to estimate the following properties for little studied materials, the method of Joback was used, (Joback and Reid 1987),

| | |
|---|---|
| $T_b$ | Boiling point, at atmospheric pressure |
| $T_c$ | Critical temperature |
| $P_c$ | Critical pressure |
| $V_c$ | Critical volume |

The chemical structure was entered into PRO/II, as described in Section 6.4.2, in the form of functional groups. The group contributions for the following properties were available within the PRO/II data base. This data is also available in the literature (Reid *et al.*, 1986, Joback and Reid, 1987):

| | |
|---|---|
| $\Delta T_b$ | Boiling point |
| $\Delta T_c$, | Critical temperature |
| $\Delta P_c$, | Critical pressure |
| $\Delta V_c$ | Critical volume |

In order to calculate the desired properties, the group contributions were found for each group making up the molecule of interest. These were substituted into the following equations:

$$T_b = 198 + \sum \Delta T_b \qquad \text{C.1}$$

$$T_c = T_b\left[0.584 + 0.965\sum \Delta T_c - \left(\sum \Delta T_c\right)^2\right]^{-1} \qquad \text{C.2}$$

$$P_c = \left(0.113 + 0.0032 n_a - \sum \Delta P_c\right)^{-2} \qquad \text{C.3}$$

$n_a$ = Number of atoms present

$$V_c = 17.5 + \sum \Delta V_c \qquad \text{C.4}$$

Knowing the critical properties, and boiling point, the acentric factor and vapour pressure can be calculated. The acentric factor is calculated using the following expresion:

$$\omega = \frac{-\ln P_c - 5.97214 + 6.09648\theta^{-1} + 1.28862\ln\theta - 0.169347\theta^6}{15.2518 - 15.6875\theta^{-1} - 13.4721\ln\theta + 0.43577\theta^6} \qquad \text{C.5}$$

$$\text{Where} \qquad \theta = \frac{T_b}{T_c}$$

To calculate the vapour pressure, $P_{VP}$ the Pitzer expression was used:

$$\ln P_{VP} = f^{(0)} + \omega f^{(1)} \qquad \text{C.6}$$

Where:

$$f^{(0)} = 5.92714 - \frac{6.09648}{T_r} - 1.28862\ln T_r + 0.169347T_r^6 \qquad \text{C.7}$$

$$f^{(1)} = 15.2518 - \frac{15.6875}{T_r} - 13.4721\ln T_r + 0.43577T_r^6 \qquad \text{C.8}$$

## Appendix D. Abbreviations Used

| | |
|---|---|
| A | Constant in equation 2.1 |
| a | Constant in cubic equation of state (equation 6.3) |
| $A^*$ | Term in equation 6.9 |
| B | Constant in equation 2.1 |
| b | Constant in cubic equation of state (equation 6.3) |
| $B^*$ | Term in equation 6.9 |
| EPA | Environmental protection act |
| f | Fugacity |
| GAS | Gas anti-solvent |
| HPMC | Hydroxypropylmethylcellulose |
| *m* | solubility (equation 2.1) |
| MM | Molar mass |
| P | Pressure |
| PCB | Polychlorinated biphenyl |
| PHB | Poly-β-hydroxybutyric acid |
| PID | Proportional, integral and derivative |
| PR | Peng Robinson |
| PTFE | Poly tetrafluroethene |
| R | Gas constant |
| RESS | Rapid expansion of supercritical solution |
| RTD | Resistance temperature device |
| $SCCO_2$ | Supercritical carbon dioxide |
| SEDS | Solvent enhanced dispersion with supercritical fluid |
| SRK | Soave Redlich Kwong |
| T | Temperature |
| u | Constant in cubic equation of state (equation 6.3) |
| UCSP | Upper critical solution pressure |
| UNIFAC | Universal functional group activity coefficients |
| UNIQUAC | Universal quasi chemical |
| USP | United States Pharmacopoeia |

| | |
|---|---|
| UV | Ultra violet |
| V | Volume |
| VOC | Volatile organic compound |
| w | Constant in cubic equation of state (equation 6.3) |
| Z | Compressibility factor |
| $\Phi$ | Fugacity coefficient |
| $\rho$ | Density |
| $\omega$ | Acentric factor |

## Superscripts

| | |
|---|---|
| $^{s}$ | Solute |
| $^{sol}$ | Solution |

## Subscripts

| | |
|---|---|
| $_{i}$ | Component i |
| $_{VPi}$ | Vapour pressure of component i |
| $_{c}$ | Critical condition |
| $_{a}$ | Initial |
| $_{f}$ | Final |
| $_{s}$ | Solute |
| $_{CO2}$ | Carbon dioxide |

## Appendix E. Units

| | |
|---|---|
| Area | square centimeters ($cm^2$) square millimeters ($mm^2$) |
| Density | $kg/m^3$, $g/cm^3$ |
| Diffusivity | $cm^2/s$ |
| Flow rate | l/min |
| Force | newtons (N) |
| Length | millimeters (mm), meters (m), Angstroms (Å), microns (μm), inches (") |
| Mass | grammes (g), kilogrammes (kg), milligrammes (mg), tonnes (t) |
| Pressure | bar, pounds per square inch (psi), atmospheres (atm) |
| Solubility | weight per cent (wt%), mole per cent (mol%), g/l |
| Stress | $N/mm^2$ |
| Temperature | degrees Celsius (°C), kelvin (K) |
| Time | hours (hr), minutes (min), seconds (s) |
| Viscosity | centipoise (cP) |
| Volume | cubic centimeters ($cm^3$), litres (l), cubic meters ($m^3$) |